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(54) Title: HUMAN PROTEINS HAVING HYDROPHOBIC DOMAINS AND DNAs ENCODING THESE PROTEINS

(57) Abstract: The present invention provides human proteins having hydrophobic domains, DNAs encoding these proteins, expression vectors for these DNAs, transformed eukaryotic cells expressing these DNAs and antibodies directed to these proteins.

DESCRIPTION

Human Proteins Having Hydrophobic Domains and DNAs Encoding These Proteins

TECHNICAL FIELD

The present invention relates to human proteins having hydrophobic domains, DNAs encoding these proteins, expression vectors for these DNAs, eukaryotic cells expressing these DNAs and antibodies directed to these proteins. The proteins of the present invention can be employed as pharmaceuticals or as antigens for preparing antibodies directed to these proteins. The human cDNAs of the present invention can be utilized as probes for genetic diagnosis and gene sources for gene therapy. Furthermore, the cDNAs can be utilized as gene sources for producing the proteins encoded by these cDNAs in large quantities. Cells into which these genes are introduced to express secretory proteins or membrane proteins in large quantities can be utilized for detection of the corresponding receptors or ligands, screening of novel small molecule pharmaceuticals and the like. The antibodies of the present invention can be utilized for the detection, quantification, purification and the like of the proteins of the present invention.

BACKGROUND ART

Cells secrete many proteins extracellularly. These secretory proteins play important roles in the proliferation control, the differentiation induction, the material transport, the biophylaxis, and the like of the cells. Unlike intracellular proteins, the secretory proteins exert their actions outside the cells. Therefore, they can be administered in the intracorporeal manner such as the injection or the drip, so that they possess hidden potentialities as pharmaceuticals. In fact, a number of human secretory proteins such as interferons, interleukins, erythropoietin, thrombolytic agents and the like are currently employed as pharmaceuticals. In addition, secretory proteins other than those described above are undergoing clinical trials for developing their use as pharmaceuticals. It is believed that the human cells produce many unknown secretory proteins. Availability of these secretory proteins as well as genes encoding them is expected to lead to development of novel pharmaceuticals utilizing them.

On the other hand, membrane proteins play important roles, as signal receptors, ion channels, transporters and the like in the material transport and the signal transduction through the cell membrane. Examples thereof include receptors for various cytokines, ion

channels for the sodium ion, the potassium ion, the chloride ion and the like, transporters for saccharides and amino acids and the like. The genes for many of them have already been cloned. It has been clarified that abnormalities in these membrane proteins are involved in a number of previously cryptogenic diseases. Therefore, discovery of a new membrane protein is expected to lead to elucidation of the causes of many diseases, so that isolation of new genes encoding the membrane proteins has been desired.

Heretofore, due to difficulty in the purification from human cells, many of these secretory proteins and membrane proteins have been isolated by genetic approaches. A general method is the so-called expression cloning method, in which a cDNA library is introduced into eukaryotic cells to express cDNAs, and the cells secreting, or expressing on the surface of membrane, the protein having the activity of interest are then screened. However, only genes for proteins with known functions can be cloned by using this method.

In general, a secretory protein or a membrane protein possesses at least one hydrophobic domain within the protein. After synthesis on ribosomes, such domain works as a secretory signal or remains in the phospholipid membrane to be entrapped in the membrane. Accordingly, if the existence of a highly hydrophobic domain is observed in the amino acid sequence of a protein encoded by a cDNA when the

whole base sequence of the full-length cDNA is determined, it is considered that the cDNA encodes a secretory protein or a membrane protein.

OBJECTS OF INVENTION

The main object of the present invention is to provide novel human proteins having hydrophobic domains, DNAs encoding these proteins, expression vectors for these DNAs, transformed eukaryotic cells that are capable of expressing these DNAs and antibodies directed to these proteins. This object as well as other objects and advantages of the present invention will become apparent to those skilled in the art from the following description with reference to the accompanying drawings.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03303.

Fig. 2 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03342.

Fig. 3 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03371.

Fig. 4 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03373.

Fig. 5 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03374.

Fig. 6 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10354.

Fig. 7 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10638.

Fig. 8 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10687.

SUMMARY OF INVENTION

As the result of intensive studies, the present inventors have successfully cloned cDNAs encoding proteins having hydrophobic domains from the human full-length cDNA bank, thereby completing the present invention. Thus, the present invention provides a human protein having hydrophobic domain(s), namely a protein comprising any one of an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 to 8. Moreover, the present invention

provides a DNA encoding said protein, exemplified by a cDNA comprising any one of a base sequence selected from the group consisting of SEQ ID NOS: 9 to 24, an expression vector that is capable of expressing said DNA by in vitro translation or in eukaryotic cells, a transformed eukaryotic cell that is capable of expressing said DNA and of producing said protein and an antibody directed to said protein.

DETAILED DESCRIPTION OF THE INVENTION

The proteins of the present invention can be obtained, for example, by a method for isolating proteins from human organs, cell lines or the like, a method for preparing peptides by the chemical synthesis based on the amino acid sequence of the present invention, or a method for producing proteins by the recombinant DNA technology using the DNAs encoding the hydrophobic domains of the present invention. Among these, the method for producing proteins by the recombinant DNA technology is preferably employed. For example, the proteins can be expressed in vitro by preparing an RNA by in vitro transcription from a vector having the cDNA of the present invention, and then carrying out in vitro translation using this RNA as a template. Alternatively, incorporation of the translated region into a suitable expression vector by the method known in the art may lead to expression of a large amount of the

encoded protein in prokaryotic cells such as *Escherichia coli*, *Bacillus subtilis*, etc., and eukaryotic cells such as yeasts, insect cells, mammalian cells, etc.

In the case where the protein of the present invention is produced by expressing the DNA by in vitro translation, the protein of the present invention can be produced in vitro by incorporating the translated region of this cDNA into a vector having an RNA polymerase promoter, and then adding the vector to an in vitro translation system such as a rabbit reticulocyte lysate or a wheat germ extract, which contains an RNA polymerase corresponding to the promoter. The RNA polymerase promoters are exemplified by T7, T3, SP6 and the like. The vectors containing promoters for these RNA polymerases are exemplified by pKA1, pCDM8, pT3/T7 18, pT7/3 19, pBluescript II and the like. Furthermore, the protein of the present invention can be expressed in the secreted form or the form incorporated in the microsome membrane when a canine pancreas microsome or the like is added to the reaction system.

In the case where the protein of the present invention is produced by expressing the DNA in a microorganism such as *Escherichia coli* etc., a recombinant expression vector in which the translated region of the cDNA of the present invention is incorporated into an expression vector having an origin which is capable of replicating in

the microorganism, a promoter, a ribosome-binding site, a cDNA-cloning site, a terminator and the like is constructed. After transformation of the host cells with this expression vector, the resulting transformant is grown, whereby the protein encoded by the cDNA can be produced in large quantities in the microorganism. In this case, a protein fragment containing any translated region can be obtained by adding an initiation codon and a termination codon in front of and behind the selected translated region to express the protein. Alternatively, the protein can be expressed as a fusion protein with another protein. Only the portion of the protein encoded by the cDNA can be obtained by cleaving this fusion protein with a suitable protease. The expression vectors for *Escherichia coli* are exemplified by the pUC series, pBluescript II, the pET expression system, the pGEX expression system and the like.

In the case where the protein of the present invention is produced by expressing the DNA in eukaryotic cells, the protein of the present invention can be produced as a secretory protein, or as a membrane protein on the surface of cell membrane, by incorporating the translated region of the cDNA into an expression vector for eukaryotic cells that has a promoter, a splicing region, a poly(A) addition site and the like, and then introducing the vector into the eukaryotic cells. The expression vectors are

exemplified by pKA1, pED6dpc2, pCDM8, pSVK3, pMSG, pSVL, pBK-CMV, pBK-RSV, EBV vectors, pRS, pYES2 and the like. Examples of eukaryotic cells to be used in general include mammalian cultured cells such as monkey kidney COS7 cells, Chinese hamster ovary CHO cells and the like, budding yeasts, fission yeasts, silkworm cells, Xenopus oocytes and the like. Any eukaryotic cells may be used as long as they are capable of expressing the proteins of the present invention. The expression vector can be introduced into the eukaryotic cells by using a method known in the art such as the electroporation method, the calcium phosphate method, the liposome method, the DEAE-dextran method and the like.

After the protein of the present invention is expressed in prokaryotic cells or eukaryotic cells, the protein of interest can be isolated and purified from the culture by a combination of separation procedures known in the art. Examples of the separation procedures include treatment with a denaturing agent such as urea or a detergent, sonication, enzymatic digestion, salting-out or solvent precipitation, dialysis, centrifugation, ultrafiltration, gel filtration, SDS-PAGE, isoelectric focusing, ion-exchange chromatography, hydrophobic chromatography, affinity chromatography, reverse phase chromatography and the like.

The proteins of the present invention also include

peptide fragments (of 5 amino acid residues or more) containing any partial amino acid sequences in the amino acid sequences represented by SEQ ID NOS: 1 to 8. These peptide fragments can be utilized as antigens for preparation of antibodies. Among the proteins of the present invention, those having the signal sequences are secreted in the form of mature proteins after the signal sequences are removed. Therefore, these mature proteins shall come within the scope of the protein of the present invention. The N-terminal amino acid sequences of the mature proteins can be easily determined by using the method for the determination of cleavage site of a signal sequence [JP-A 8-187100]. Furthermore, some membrane proteins undergo the processing on the cell surface to be converted to the secreted forms. Such proteins or peptides in the secreted forms shall also come within the scope of the protein of the present invention. In the case where sugar chain-binding sites are present in the amino acid sequences of the proteins, expression of the proteins in appropriate eukaryotic cells affords the proteins to which sugar chains are added. Accordingly, such proteins or peptides to which sugar chains are added shall also come within the scope of the protein of the present invention.

The DNAs of the present invention include all the DNAs encoding the above-mentioned proteins. These DNAs can

be obtained by using a method for chemical synthesis, a method for cDNA cloning and the like.

The cDNAs of the present invention can be cloned, for example, from cDNA libraries derived from the human cells. The cDNAs are synthesized by using poly(A)$^+$ RNAs extracted from human cells as templates. The human cells may be cells delivered from the human body, for example, by the operation or may be the cultured cells. The cDNAs can be synthesized by using any method such as the Okayama-Berg method [Okayama, H. and Berg, P., Mol. Cell. Biol. 2: 161-170 (1982)], the Gubler-Hoffman method [Gubler, U. and Hoffman, J., Gene 25: 263-269 (1983)] and the like. However, it is desirable to use the capping method [Kato, S. et al., Gene 150: 243-250 (1994)], as exemplified in Examples, in order to obtain a full-length clone in an effective manner. In addition, commercially available human cDNA libraries can be utilized. The cDNAs of the present invention can be cloned from the cDNA libraries by synthesizing an oligonucleotide on the basis of base sequences of any portion in the cDNA of the present invention and screening the cDNA libraries using this oligonucleotide as a probe for colony or plaque hybridization according to a method known in the art. In addition, the cDNA fragments of the present invention can be prepared from an mRNA isolated from human cells by the RT-PCR method in which oligonucleotides which

hybridize with both termini of the cDNA fragment of interest are synthesized, which are then used as the primers.

The cDNAs of the present invention are characterized in that they comprise any one of the base sequences represented by SEQ ID NOS: 9 to 16 or the base sequences represented by SEQ ID NOS: 17 to 24. Table 1 summarizes the clone number (HP number), the cells from which the cDNA clone was obtained, the total number of bases of the cDNA, and the number of the amino acid residues of the encoded protein, for each of the cDNAs.

Table 1

SEQ ID NO	HP number	Cell	Number of bases	Number of amino acid residues
1, 9, 17	HP03303	Liver	1167	238
2, 10, 18	HP03342	Umbilical cord blood	1925	339
3, 11, 19	HP03371	PMA-U937	1125	326
4, 12, 20	HP03373	Umbilical cord blood	1734	324
5, 13, 21	HP03374	Umbilical cord blood	2064	153
6, 14, 22	HP10354	Stomach cancer	570	153
7, 15, 23	HP10638	Stomach cancer	1161	200
8, 16, 34	HP10687	Thymus	823	189

The same clones as the cDNAs of the present invention can be easily obtained by screening the cDNA libraries constructed from the human cell lines or human tissues utilized in the present invention using an oligonucleotide probe synthesized on the basis of the base sequence of the cDNA provided in any one of SEQ ID NOS: 9 to 24.

In general, the polymorphism due to the individual differences is frequently observed in human genes. Accordingly, any cDNA in which one or plural nucleotides are added, deleted and/or substituted with other nucleotides in SEQ ID NOS: 9 to 24 shall come within the scope of the present invention.

Similarly, any protein in which one or plural amino acids are added, deleted and/or substituted with other

amino acids resulting from the above-mentioned changes shall come within the scope of the present invention, as long as the protein possesses the activity of the protein having any one of the amino acid sequences represented by SEQ ID NOS: 1 to 8.

The cDNAs of the present invention also include cDNA fragments (of 10 bp or more) containing any partial base sequence in the base sequences represented by SEQ ID NOS: 9 to 16 or in the base sequences represented by SEQ ID NOS: 17 to 24. Also, DNA fragments consisting of a sense strand and an anti-sense strand shall come within this scope. These DNA fragments can be utilized as the probes for the genetic diagnosis.

The antibody of the present invention can be obtained from a serum after immunizing an animal using the protein of the present invention as an antigen. A peptide that is chemically synthesized based on the amino acid sequence of the present invention and a protein expressed in eukaryotic or prokaryotic cells can be used as an antigen. Alternatively, an antibody can be prepared by introducing the above-mentioned expression vector for eukaryotic cells into the muscle or the skin of an animal by injection or by using a gene gun and then collecting a serum therefrom (JP-A 7-313187). Animals that can be used include a mouse, a rat, a rabbit, a goat, a chicken and the like. A monoclonal

antibody directed to the protein of the present invention can be produced by fusing B cells collected from the spleen of the immunized animal with myelomas to generate hybridomas.

In addition to the activities and uses described above, the polynucleotides and proteins of the present invention may exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA

sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological

fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present

invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9,

B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ, Schreiber, R.D. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons,

Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6- Nordan, R. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark,S.C. and Turner, K.J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by

measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or

other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an

immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the

transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic

pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in

preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a

soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells in vivo.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in

expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation

of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowmanet al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin

responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: In vitro antibody production, Mond, J.J. and Brunswick, M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of

Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complementary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic

utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays,

Freshney, M.G. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces

cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue

or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon);

International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from

cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized

infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-

Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke)).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-

474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek,

D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis,

complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria,

viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or cardiac cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response

against such protein or another material or entity which is cross-reactive with such protein.

Examples

The present invention is specifically illustrated in more detail by the following Examples, but Examples are not intended to restrict the present invention. The basic procedures with regard to the recombinant DNA and the enzymatic reactions were carried out according to the literature ["Molecular Cloning. A Laboratory Manual", Cold Spring Harbor Laboratory, 1989]. Unless otherwise stated, restriction enzymes and various modifying enzymes to be used were those available from Takara Shuzo. The buffer compositions and the reaction conditions for each of the enzyme reactions were as described in the attached instructions. The cDNA synthesis was carried out according to the literature [Kato, S. et al., Gene 150: 243-250 (1994)].

(1) Selection of cDNAs Encoding Proteins Having Hydrophobic Domains

The cDNA library of stomach cancer tissue (WO98/21328) and the cDNA library of liver tissue (WO98/21328) were used as cDNA libraries. Additionally, the cDNA libraries constructed from phorbol ester-stimulated

histiocytic lymphoma cell line U937 (ATCC CRL 1593) mRNA, human thymus mRNA (Clontech) and human umbilical cord blood mRNA were also used. Full-length cDNA clones were selected from the respective libraries and the whole base sequences thereof were determined to construct a homo-protein cDNA bank consisting of the full-length cDNA clones. The hydrophobicity/hydrophilicity profiles were determined for the proteins encoded by the full-length cDNA clones registered in the homo-protein cDNA bank by the Kyte-Doolittle method [Kyte, J. & Doolittle, R. F., J. Mol. Biol. 157: 105-132 (1982)] to examine the presence or absence of a hydrophobic domain. A clone that has a hydrophobic region being assumed as a secretory signal or a transmembrane domain in the amino acid sequence of the encoded protein was selected as a clone candidate.

(2) Protein Synthesis by In Vitro Translation

The plasmid vector bearing the cDNA of the present invention was used for in vitro transcription/translation with a T_NT rabbit reticulocyte lysate kit (Promega). In this case, [^{35}S]methionine was added to label the expression product with a radioisotope. Each of the reactions was carried out according to the protocols attached to the kit. Two micrograms of the plasmid was subjected to the reaction at 30°C for 90 minutes in the reaction solution of a total volume of 25 µl containing 12.5 µl µ of T_NT rabbit

reticulocyte lysate, 0.5 µl of a buffer solution (attached to the kit), 2 µl of an amino acid mixture (without methionine), 2 µl of [^{35}S]methionine (Amersham) (0.37 MBq/µl), 0.5 µl of T7 RNA polymerase, and 20 U of RNasin. The experiment in the presence of a membrane system was carried out by adding 2.5 µl of a canine pancreas microsome fraction (Promega) to the reaction system. To 3 µl of the reaction solution was added 2 µl of the SDS sampling buffer (125 mM Tris-hydrochloride buffer, pH 6.8, 120 mM 2-mercaptoethanol, 2% SDS solution, 0.025% bromophenol blue and 20% glycerol) and the resulting mixture was heated at 95°C for 3 minutes and then subjected to SDS-polyacrylamide gel electrophoresis. The molecular weight of the translation product was determined by carrying out the autoradiography.

(3) Expression in COS7

Escherichia coli cells harboring the expression vector for the protein of the present invention were cultured at 37°C for 2 hours in 2 ml of the 2 x YT culture medium containing 100 µg/ml of ampicillin, the helper phage M13KO7 (50 µl) was added thereto, and the cells were then cultured at 37°C overnight. Single-stranded phage particles were obtained by polyethylene glycol precipitation from a supernatant separated by centrifugation. The particles were suspended in 100 µl of 1 mM Tris-0.1 mM EDTA, pH 8 (TE).

The cultured cells derived from monkey kidney,

COS7, were cultured at 37°C in the presence of 5% CO_2 in the Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal calf serum. 1 x 10^5 COS7 cells were inoculated into a 6-well plate (Nunc, well diameter: 3 cm) and cultured at 37°C for 22 hours in the presence of 5% CO_2. After the medium was removed, the cell surface was washed with a phosphate buffer solution followed by DMEM containing 50 mM Tris-hydrochloride (pH 7.5) (TDMEM). A suspension containing 1 µl of the single-stranded phage suspension, 0.6 ml of the DMEM medium and 3 µl of TRANSFECTAM™ (IBF) was added to the cells and the cells were cultured at 37°C for 3 hours in the presence of 5% CO_2. After the sample solution was removed, the cell surface was washed with TDMEM, 2 ml per well of DMEM containing 10% fetal calf serum was added, and the cells were cultured at 37°C for 2 days in the presence of 5% CO_2. After the medium was exchanged for a medium containing [^{35}S]cysteine or [^{35}S]methionine, the cells were cultured for one hour. After the medium and the cells were separated each other by centrifugation, proteins in the medium fraction and the cell membrane fraction were subjected to SDS-PAGE.

(4) Preparation of Antibodies

A plasmid vector containing the cDNA of the present invention was dissolved in a phosphate buffer solution (PBS: 145 mM NaCl, 2.68 mM KCl, 8.09 mM Na_2HPO_4, 2 mM KH_2PO_4, pH 7.2) to a concentration of 2 µg/µl. 25 µl each

(a total of 50 µl) of the thus-prepared plasmid solution in PBS was injected into the right and left musculi quadriceps femoris of three mice (ICR line) using a 26 guage needle. After similar injections were repeated for one month at intervals of one week, blood was collected. The collected blood was stored at 4°C overnight to coagulate the blood, and then centrifuged at 8,000 x g for five minutes to obtain a supernatant. NaN_3 was added to the supernatant to a concentration of 0.01% and the mixture was then stored at 4°C. The generation of an antibody was confirmed by immunostaining of COS7 cells into which the corresponding vector had been introduced or by Western blotting using a cell lysate or a secreted product.

(5) Clone Examples

<HP03303> (SEQ ID NOS: 1, 9, and 17)

Determination of the whole base sequence of the cDNA insert of clone HP03303 obtained from cDNA library of human liver revealed the structure consisting of a 186-bp 5'-untranslated region, a 717-bp ORF, and a 264-bp 3'-untranslated region. The ORF encodes a protein consisting of 238 amino acid residues and there existed one transmembrane domain at the N-terminus. Figure 1 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product

of 27 kDa that was almost identical with the molecular weight of 27,141 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 29 kDa to which sugar chains are presumably added. In addition, there exists in the amino acid sequence of this protein one site at which N-glycosylation may occur (Asn-Phe-Thr at position 29).

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to human hypothetical protein KIAA1007 (GenBank Accession No. AB023224). The C-terminal region starting from position 14 of the human protein of the present invention completely matched with the C-terminal region starting from position 865 of human hypothetical protein KIAA1007.

<HP03342> (SEQ ID NOS: 2, 10, and 18)

Determination of the whole base sequence of the cDNA insert of clone HP03342 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 114-bp 5'-untranslated region, a 1020-bp ORF, and a 791-bp 3'-untranslated region. The ORF encodes a protein consisting of 339 amino acid residues and there existed at the N-terminus a putative secretory signal and one transmembrane domain. Figure 2 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-

Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 34 kDa that was somewhat smaller than the molecular weight of 36,952 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to Caenorhabditis elegans hypothetical protein CET06D8.9 (GenBank Protein ID No. CAA88972). Table 2 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and Caenorhabditis elegans hypothetical protein CET06D8.9 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 35.0% in the entire region.

Table 2

```
HP  MAAACGPGAAGYCLLLGLHLFLLTAGPALGWNDPDRMLLRDVKALTLHYDRYTTSRRLD
                                .*..*****.*.*** .. **.**..
CE  MSNKGVAMISRFTTSFLLWMLLVFTVVFFETSAASDKVLLRDVSAITLHKGKMTTGRRVS

HP  PIPQLKCVGGTAGCDSYTPKVIQCQNKGWDGYDVQWECKTDLDIAYKFGKTVVSCEGYES
```

```
   *. *******.*  ...****.**.*.*.** **** *..**  . .**.. ******.
CE PTFQLKCVGGSAK GAFTPKVVQCANQGFDGSDVQWRCDADLPHDMEFGSISVSCEGYDY

HP SEDQYVLRGSCGLEYNLDY TELGLQKLKESGKQHGFASFSDY YYKWSSADSCNMSGLI
   .**.*.*********.*.* .. * .... ...*. .. *...    . .   ..* .
CE AEDPYILRGSCGLEYELEYNSASGNRSVSRKSSQDRWDQFATFVVVAFIAYIIYAMWTNR

HP TIVVLLGIAFVVYKLFLSDGQYSPPPYSEYPPFSHRYQRFTNSAGPPPPGFKSEFTGPQN
   .     . ...      ..*. *    ..   ..   ..... . *** **...   .*.
CE NQNP ESSGYTSGGSGGPGGPGSGGGGGGPGGYPSAPPPYDDYSKPPPYGFRGD   SQS

HP TGHGATSGFGSAFTGQQGYENSGPGFWTGLGTGGILGYLFGS NRAATPFSDSWYYPSYP
   .* ..*. *.*  .  * .*.* .**** . *.* *** .* ..... ..* ...
CE GGGCQGSSSGGA  SGSG ANNGGSFWTGASLGAIGGYLASSFLNNNNAYARPRYNRGF

HP PSYPGTWNRAYSPLHGGSGSYSVCSNSDTKTRTASGYGGTRRR
     ...*   ..*    .*.*.*  * *... *..****** **
CE   FQDT   GFS    SSDSWS  SPSTSSMRSSSGYGGTTRR
```

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. W02871) among ESTs. However, since they are partial sequences, it can not be judged

whether or not they encode the same protein as the protein of the present invention.

<HP03371> (SEQ ID NOS: 3, 11, and 19)

Determination of the whole base sequence of the cDNA insert of clone HP03371 obtained from cDNA library of human lymphoma cell line U937 revealed the structure consisting of a 70-bp 5'-untranslated region, a 981-bp ORF, and a 74-bp 3'-untranslated region. The ORF encodes a protein consisting of 326 amino acid residues and there existed two putative transmembrane domains. Figure 3 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 39 kDa that was somewhat larger than the molecular weight of 36,717 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to mouse GSG1 (GenBank Protein ID No. BAA37087.1). Table 3 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and mouse GSG1 (MM). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology

of 71.5% in the entire region.

Table 3

```
HP MAKMELSKAFSGQRTLLSAILSMLSLSFSTTSLLSNYWFVGTQKVPKPLCEKGLAAKCFD
      **. *. *. ***. . ****. ****. . **. ****. ************. . . *******
MM    MEFQKGSSDQRTFISAILNMLSLGLSTASLLSSEWFVGTQKVPKPLCGQSLAAKCFD

HP MPVSLDGD-TNTSTQEVVQYNWETGDDRFSFRSFRSGMWLSCEETVEEPGERCRSFIELT
   **. ****. . ***. ******. ********** . ************. *****. **. *****
MM MPMSLDGGIANTSAQEVVQYTWETGDDRFSFLAFRSGMWLSCEETMEEPGEKCRRFIELT

HP PPAKR----------------------------------------EILWLSLGTQITYI
   ***. *                                        . . . *****. *. . **
MM PPAQRGEKGLLEFATLQGSCHPTLRFGGEWLMEKASLLHLPWGPVAKVFWLSLGAQTAYI

HP GLQFISFLLLLTDLLLTGNPACGLKLSAFAAVSSVLSGLLGMVAHMMYSQVFQATVNLGP
   ***. **********. **. ********** ********** ********. ****
MM GLQLISFLLLLTDLLLTTNPGCGLKLSAFAAVSLVLSGLLGMVAHMLYSQVFQATANLGP

HP EDWRPHVWNYGWAFYMAWLSFTCCM-ASAVTTFNTYTRMVLEFKCKHSKSFKENPNCLPH
   *  . . .  .. .  ..*  . . . ***** **********. *****. . **. **. *
MM E-LETTLLELRLGL-LHSVGFLHLLHGVTVTTFNMYTRMVLEFKCRHSKSFNTNPSCLAH

HP HHQCFPRRLSSAAPTVGPLTSYHQYHNQPIHSVSEGVDFYSELRNKGFQRGASQELKEAV
```

MM TTAVSFLLR

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA406443) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03373> (SEQ ID NOS: 4, 12, and 20)

Determination of the whole base sequence of the cDNA insert of clone HP03373 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 39-bp 5'-untranslated region, a 975-bp ORF, and a 720-bp 3'-untranslated region. The ORF encodes a protein consisting of 324 amino acid residues and there existed six putative transmembrane domains. Figure 4 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein revealed that the

protein was similar to mouse transmembrane protein PFT27 (SWISSPROT Accession No. P52875). Table 4 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and mouse transmembrane protein PFT27 (MM). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 90.1% in the entire region.

Table 4

```
HP MAAAAPGNGRASAPRLLLLFLVPLLWAPAAVRAGPDEDLSHRNKEPPAPAQQLQPQPVAV
   *****.*.***...***.*.*..******.*****.*******.*****.     ***.**
MM MAAAARGSGRAPTRRLLVLLLLQLLWAPAGVRAGPEEDLSHRNQEPPAPPSSCSPQPAAV

HP QGPEPARVEKIFTPAAPVHTNKEDPATQTNLGFIHAFVAAISVIIVSELGDKTFFIAAIM
   ** ****.** .**.**********.*.**********************************
MM QGLEPARAEKGLTPVAPVHTNKEDAAAQTNLGFIHAFVAAISVIIVSELGDKTFFIAAIM

HP AMRYNRLTVLAGAMLALGLMTCLSVLFGYATTVIPRVYTYYVSTVLFAIFGIRMLREGLK
   ****************.**************************.***************
MM AMRYNRLTVLAGAMLALALMTCLSVLFGYATTVIPRVYTYYVSTALFAIFGIRMLREGLK
```

```
HP MSPDEGQEELEEVQAELKKKDEEFQRTKLLNGPGDVETGTSITVPQKKWLHFISPIFVQA
   ********************************** *******...**********************
MM MSPDEGQEELEEVQAELKKKDEEFQRTKLLNGP DVETGTSTAIPQKKWLHFISPIFVQA

HP LTLTFLAEWGDRSQLTTIVLAAREDPYGVAVGGTVGHCLCTGLAVIGGRMIAQKISVRTV
   ************************************************************
MM LTLTFLAEWGDRSQLTTIVLAAREDPYGVAVGGTVGHCLCTGLAVIGGRMIAQKISVRTV

HP TIIGGIVFLAFAFSALFISPDSGF
   ********************. ***
MM TIIGGIVFLAFAFSALFISPESGF
```

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI358154) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03374> (SEQ ID NOS: 5, 13, and 21)

Determination of the whole base sequence of the cDNA insert of clone HP03374 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 97-bp 5'-untranslated region, a 462-bp ORF, and a 1505-

bp 3'-untranslated region. The ORF encodes a protein consisting of 153 amino acid residues and there existed one putative transmembrane domain. Figure 5 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 20 kDa that was somewhat larger than the molecular weight of 17,483 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to Schizosaccharomyces pombe hypothetical protein SPBC119.09c (GenBank Protein ID No. CAA17924). Table 5 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and Schizosaccharomyces pombe hypothetical protein SPBC119.09c (SP). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 44.1% in the entire region.

Table 5

HP	MNVGTAHSEVNPNTRVMNSRGIWLSYVLAIGLLHIVLL

```
                                        .* .* *. ... *. *....
SP MGSSSSRRRSSSLVTKVPKPTIDDRLDQGSATNYNSNWVNYKGAWVIHIVLIAALRLIFH

HP SIPFVSVPVVWTLTNLIHNMGMYIFLHTVKGTPFETPDQGKARLLTHWEQMDYGVQFTAS
   .** **  ..******..  * .*..* *.*****  . . .* ** ***.* * *.*..
SP AIPSVSRELAWTLTNLTYMAGSFIMFHWVTGTPFEFNGGAYDR LTMWEQLDEGNQYTPA

HP RKFLTITPIVLYFLTSFYTKYDQIHFVLNTVSLMSVLIPKLPQLHGVRIFGINKY
   **.* . **.*..... **.*.   *..*. .*. *******..*  *****.*
SP RKYLLVLPIILFLMSTHYTHYNGWMFLVNIWALFMVLIPKLPAVHRKRIFGIQKLSLRDD
```

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA889229) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10354> (SEQ ID NOS: 6, 14, and 22)

Determination of the whole base sequence of the cDNA insert of clone HP10354 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 27-bp 5'-untranslated region, a 462-bp ORF, and a 81-bp 3'-untranslated region. The ORF encodes a protein consisting of

153 amino acid residues and there existed one putative transmembrane domain. Figure 6 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 18 kDa that was somewhat larger than the molecular weight of 17,352 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to Schizosaccharomyces pombe hypothetical protein SPBC119.09c (GenBank Protein ID No. CAA17924). Table 6 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and Schizosaccharomyces pombe hypothetical protein SPBC119.09c (SP). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 41.9% in the entire region.

Table 6

HP	MNVGTAHSEVNPNTRVMNSRGIWLSYVLAIGLLHIVLL
	.* .* *. ... *. *....

SP MGSSSSRRRSSSLVTKVPKPTIDDRLDQGSATNYNSNWVNYKGAWVIHIVLIAALRLIFH

HP SIPFVSVPVVWTLTNLIHNMGMYIFLHTVKGTPFETPDQGKARLLTHWEQMDYGVQFTAS

.** ** ..******.. * .*..* *.***** . . .* ** ***.* * *.*..

SP AIPSVSRELAWTLTNLTYMAGSFIMFHWVTGTPFEFNGGAYDR LTMWEQLDEGNQYTPA

HP RKFLTITPIVLYFLTSFYTKYDQIHFVLNTVSLMSVLIPKLPQLHGVRIFGINKY

.* . **.*..... **.*. *..*. .*. *****..* *****.*

SP RKYLLVLPIILFLMSTHYTHYNGWMFLVNIWALFMVLIPKLPAVHRKRIFGIQKLSLRDD

The present protein was also similar to the protein of the present invention, HP03374. Table 7 shows the comparison between amino acid sequences of the present protein (HP) and HP03374 (HS). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 81.0% in the entire region.

Table 7

HP MNVGVAHSEVNPNTRVMNSRGIWLAYIILVGLLHMVLLSIPFFSIPVVWTLTNVIHNLAT

****.******************.*.. .****.******* *.********.***..

```
HS MNVGTAHSEVNPNTRVMNSRGIWLSYVLAIGLLHIVLLSIPFVSVPVVWTLTNLIHNMGM

HP YVFLHTVKGTPFETPDQGKARLLTHWEQMDYGLQFTSSRKFLSISPIVLYLLASFYTKYD
   *. ********************************. ***. *****. *. *****. *. *******
HS YIFLHTVKGTPFETPDQGKARLLTHWEQMDYGVQFTASRKFLTITPIVLYFLTSFYTKYD

HP AAHFLINTASLLSVLLPKLPQFHGVRVFGINKY
   . **. . **. **. ***. *****. ****. ******
HS QIHFVLNTVSLMSVLIPKLPQLHGVRIFGINKY
```

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA179187) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10638> (SEQ ID NOS: 7, 15, and 23)

Determination of the whole base sequence of the cDNA insert of clone HP10638 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 277-bp 5'-untranslated region, a 603-bp ORF, and a 281-bp 3'-untranslated region. The ORF encodes a protein consisting of 200 amino acid residues and there existed at least one

putative transmembrane domain. Figure 7 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 23 kDa that was almost identical with the molecular weight of 22,751 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. N36033) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10687> (SEQ ID NOS: 8, 16, and 24)

Determination of the whole base sequence of the cDNA insert of clone HP10687 obtained from cDNA library of human thymus revealed the structure consisting of a 57-bp 5'-untranslated region, a 570-bp ORF, and a 196-bp 3'-untranslated region. The ORF encodes a protein consisting of 189 amino acid residues and there existed a secretory signal at the N-terminus. Figure 8 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 23 kDa that was somewhat larger than the molecular weight

of 20,681 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 21 kDa. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from aspartic acid at position 23.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA215334) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

INDUSTRIAL APPLICABILITY

The present invention provides human proteins having hydrophobic domains, DNAs encoding these proteins, expression vectors for these DNAs and eukaryotic cells expressing these DNAs. Since all of the proteins of the present invention are secreted or exist in the cell membrane, they are considered to be proteins controlling the proliferation and/or the differentiation of the cells. Accordingly, the proteins of the present invention can be employed as pharmaceuticals such as carcinostatic agents which act to control the proliferation and/or the

differentiation of the cells, or as antigens for preparing antibodies against these proteins. The DNAs of the present invention can be utilized as probes for the genetic diagnosis and gene sources for the gene therapy. Furthermore, the DNAs can be utilized for expressing these proteins in large quantities. Cells into which these genes are introduced to express these proteins can be utilized for detection of the corresponding receptors or ligands, screening of novel small molecule pharmaceuticals and the like. The antibody of the present invention can be utilized for the detection, quantification, purification and the like of the protein of the present invention.

The present invention also provides genes corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which cDNA polynucleotide sequences are derived and may include contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or

primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Morris, 1994, Trends Pharmacol. Sci. 15(7): 250-254; Lavarosky et al., 1997, Biochem. Mol. Med. 62(1): 11-22; and Hampel, 1998, Prog. Nucleic Acid Res. Mol. Biol. 58: 1-39; all of which are incorporated by reference herein). Transgenic animals that have multiple copies of the gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1,

incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to the polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, Bioessays 14(9): 629-633; Zwaal et al., 1993, Proc. Natl. Acad. Sci. USA 90(16): 7431-7435; Clark et al., 1994, Proc. Natl. Acad. Sci. USA 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination, preferably detected by positive/negative genetic selection strategies (Mansour et al., 1988, Nature 336: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614, 396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s). Where the protein of the present invention is

membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment

of any of the disclosed proteins.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide, as determined by those of skill in the art. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous, or related to that encoded by the polynucleotides.

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency

conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

Table 8

Stringency Condition	Poly-nucleotide Hybrid	Hybrid Length (bp)'	Hybridization Temperature and Buffer'	Wash Temperature and Buffer'
A	DNA : DNA	≥50	65°C; 1×SSC -or- 42°C; 1×SSC, 50% formamide	65°C; 0.3×SSC
B	DNA : DNA	<50	T_B*; 1×SSC	T_B*; 1×SSC
C	DNA : RNA	≥50	67°C; 1×SSC -or- 45°C; 1×SSC, 50% formamide	67°C; 0.3×SSC
D	DNA : RNA	<50	T_D*; 1×SSC	T_D*; 1×SSC
E	RNA : RNA	≥50	70°C; 1×SSC -or- 50°C; 1×SSC, 50% formamide	70°C; 0.3×SSC
F	RNA : RNA	<50	T_F*; 1×SSC	T_F*; 1×SSC
G	DNA : DNA	≥50	65°C; 4×SSC -or- 42°C; 4×SSC, 50% formamide	65°C; 1×SSC
H	DNA : DNA	<50	T_H*; 4×SSC	T_H*; 4×SSC
I	DNA : RNA	≥50	67°C; 4×SSC -or- 45°C; 4×SSC, 50% formamide	67°C; 1×SSC
J	DNA : RNA	<50	T_J*; 4×SSC	T_J*; 4×SSC
K	RNA : RNA	≥50	70°C; 4×SSC -or- 50°C; 4×SSC, 50% formamide	67°C; 1×SSC
L	RNA : RNA	<50	T_L*; 2×SSC	T_L*; 2×SSC
M	DNA : DNA	≥50	50°C; 4×SSC -or- 40°C; 6×SSC, 50% formamide	50°C; 2×SSC
N	DNA : DNA	<50	T_N*; 6×SSC	T_N*; 6×SSC
O	DNA : RNA	≥50	55°C; 4×SSC -or- 42°C; 6×SSC, 50% formamide	55°C; 2×SSC
P	DNA : RNA	<50	T_P*; 6×SSC	T_P*; 6×SSC
Q	RNA : RNA	≥50	60°C; 4×SSC -or- 45°C; 6×SSC, 50% formamide	60°C; 2×SSC
R	RNA : RNA	<50	T_R*; 4×SSC	T_R*; 4×SSC

‡ : The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

† : SSPE (1×SSPE is 0.15M NaCl, 10mM NaH_2PO_4, and 1.25mM EDTA, pH7.4) can be substituted for SSC (1×SSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

*T_B - T_R : The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, T_m(°C)=2(#of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T_m(°C)=81.5 + 16.6($\log_{10}$[Na^+]) + 0.41 (%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na^+] is the concentration of sodium ions in the hybridization buffer ([Na^+] for 1×SSC=0.165M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and Current Protocols in Molecular Biology, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

CLAIMS

1. A protein comprising any one of an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 to 8.

2. An isolated DNA encoding the protein according to Claim 1.

3. An isolated cDNA comprising any one of a base sequence selected from the group consisting of SEQ ID NOS: 9 to 16.

4. The cDNA according to Claim 3 consisting of any one of a base sequence selected from the group consisting of SEQ ID NOS: 17 to 24.

5. An expression vector that is capable of expressing the DNA according to any one of Claim 2 to Claim 4 by in vitro translation or in eukaryotic cells.

6. A transformed eukaryotic cell that is capable of expressing the DNA according to any one of Claim 2 to Claim 4 and of producing the protein according to Claim 1.

7. An antibody directed to the protein according to Claim 1.

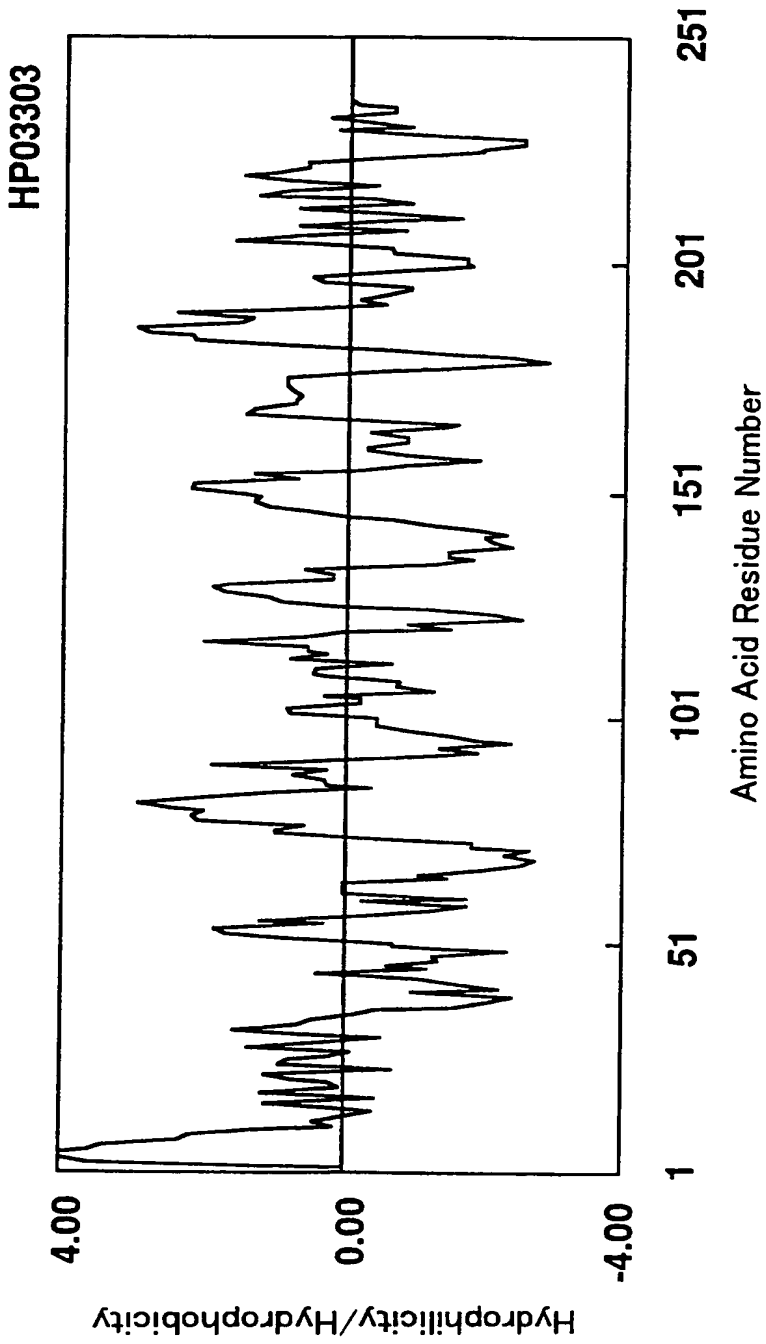
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Fig.1

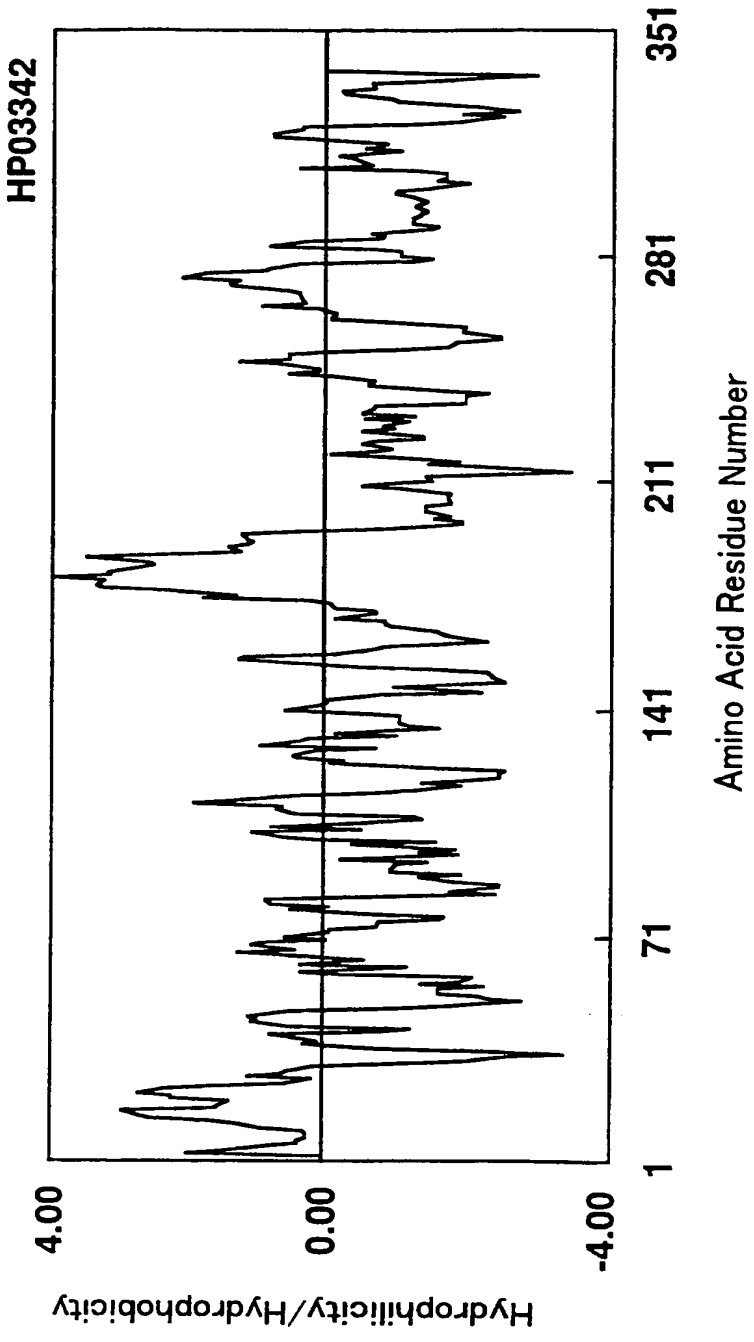
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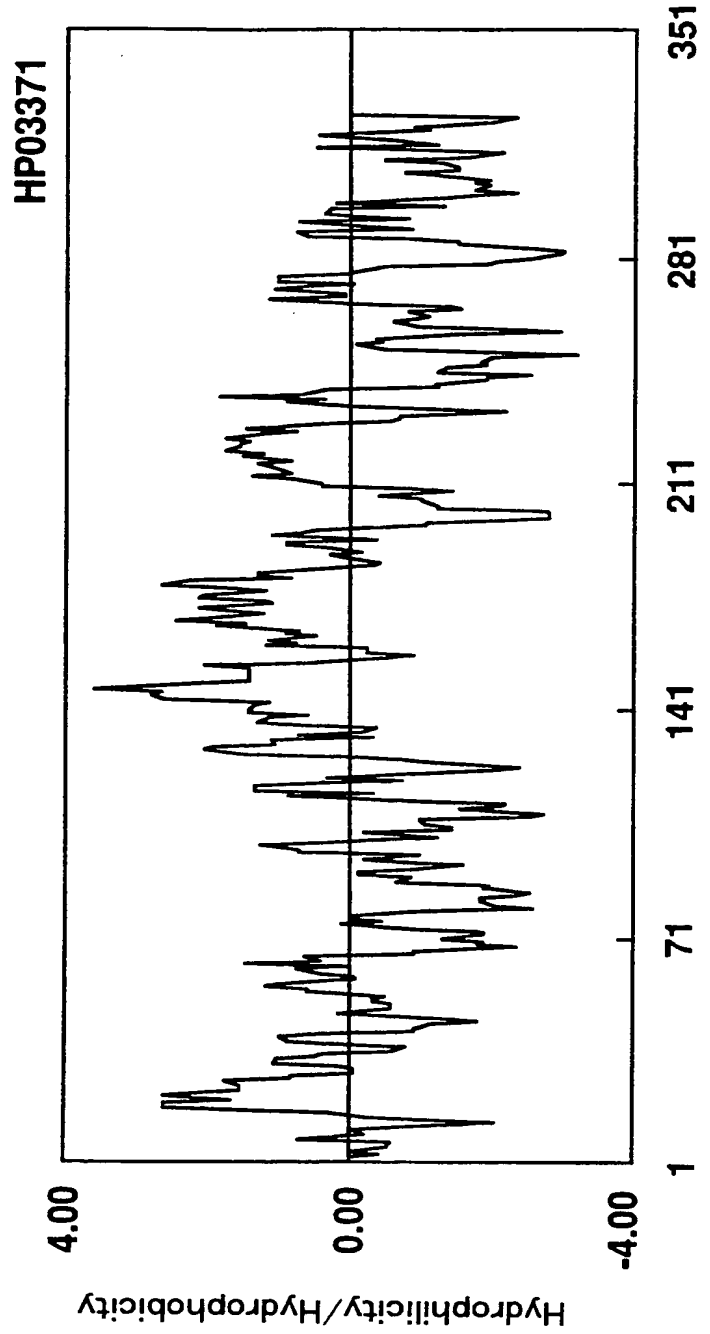
Fig.2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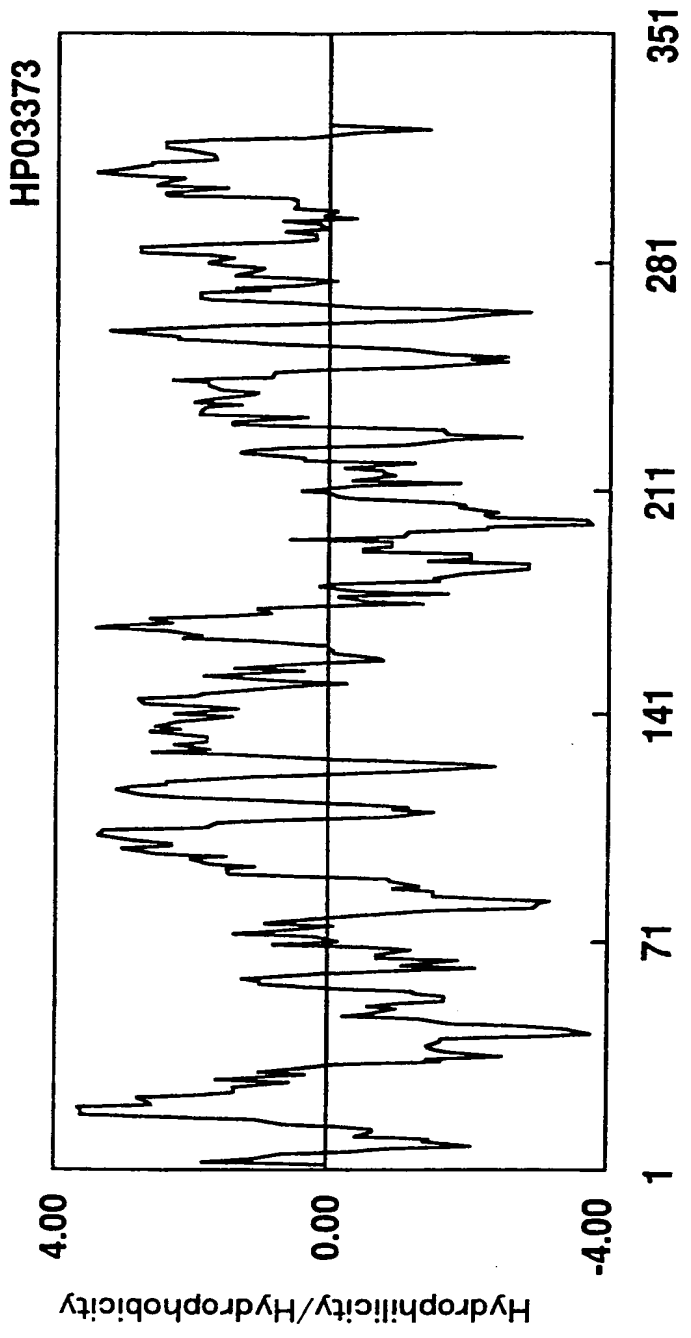
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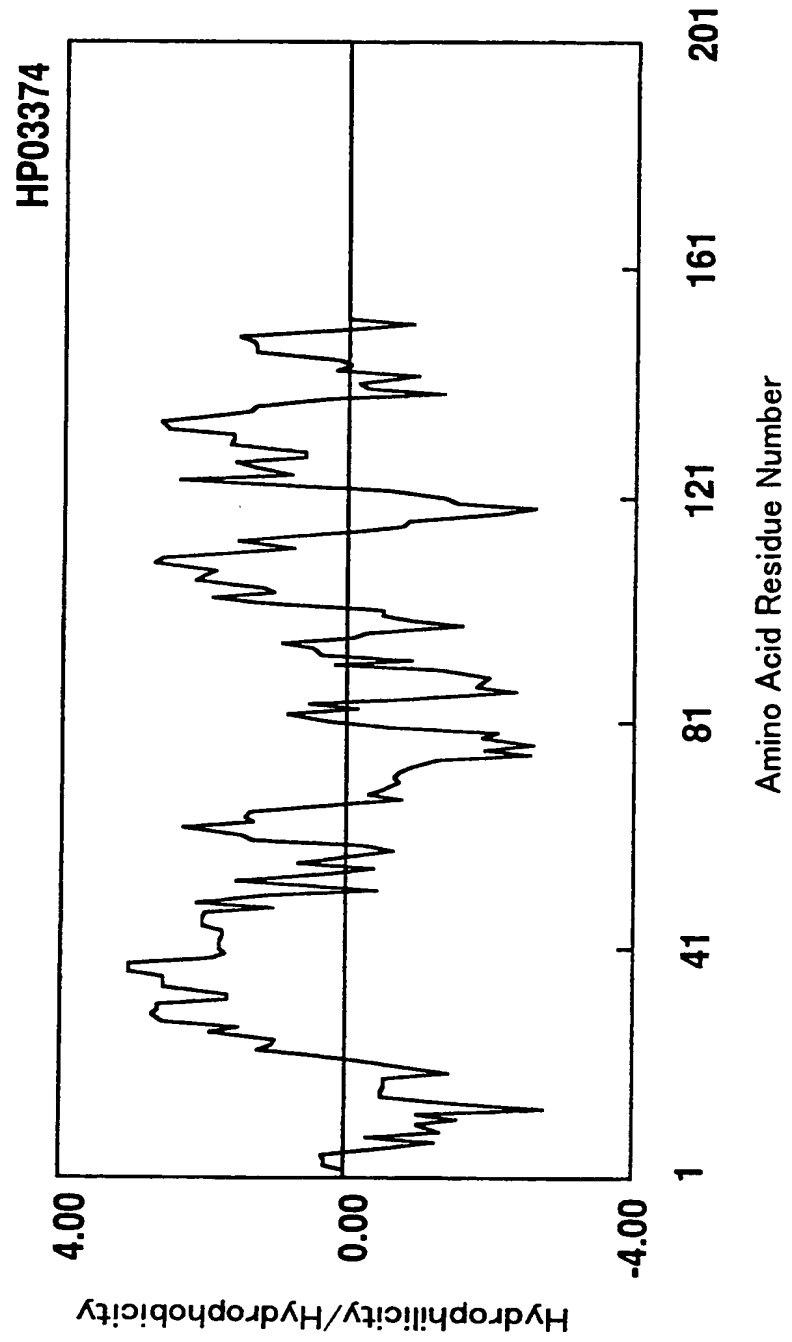
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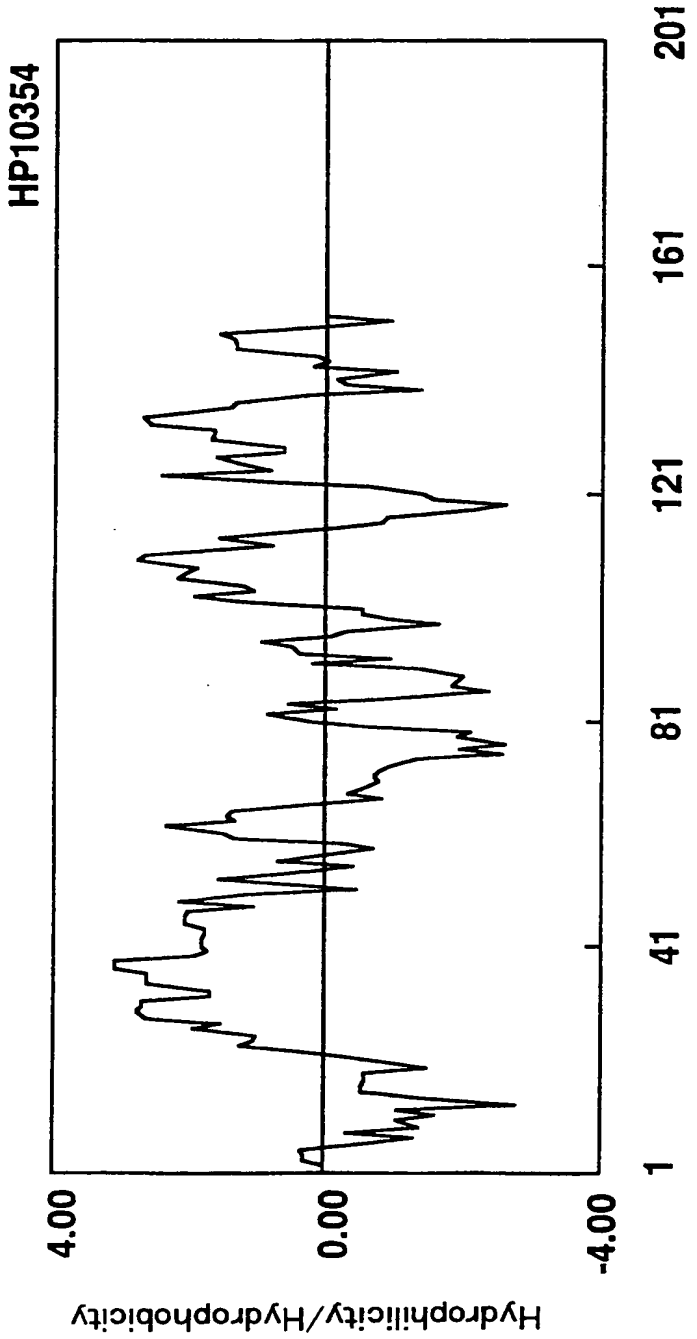
Fig.5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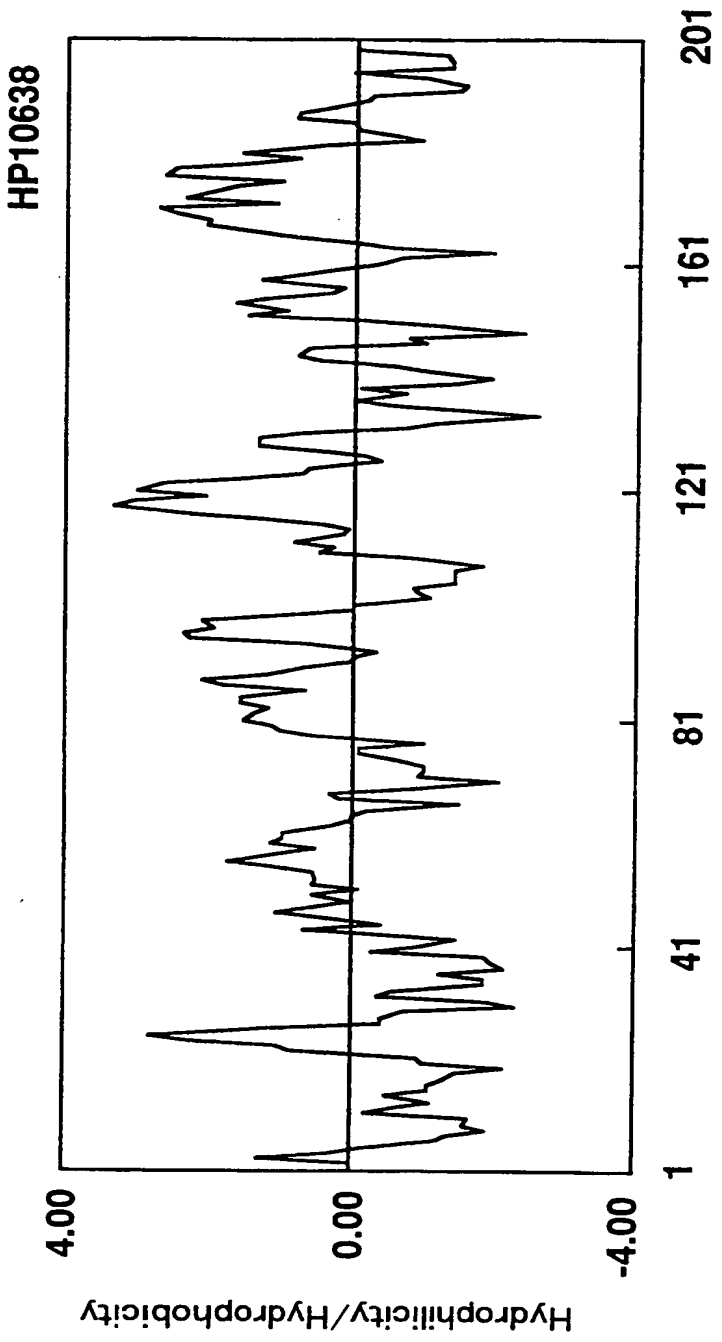
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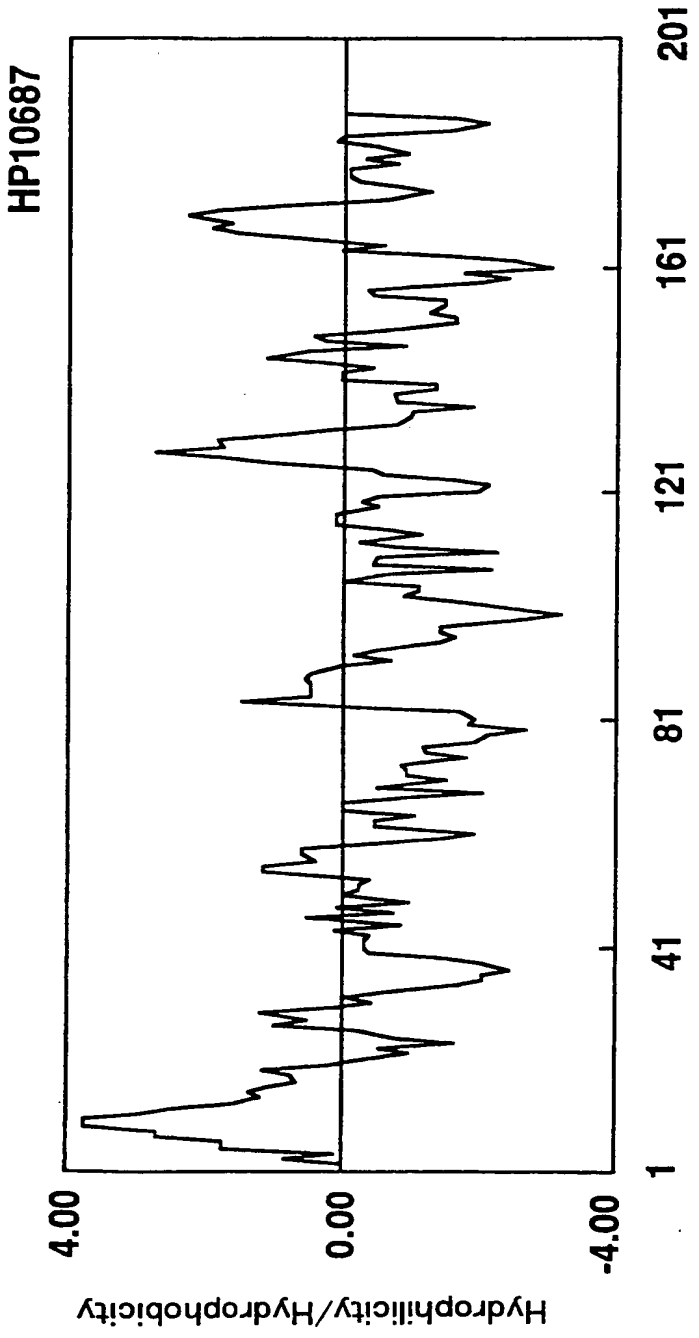
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Fig.8

SEQUENCE LISTING

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Protegene Inc.

<120> Human proteins having hydrophobic domains and DNAs encoding these proteins

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<150> JP 11-178065

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35 40 45

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50 55 60

Ser Asn Glu Pro Gly Asn Arg Tyr Asn Leu Gln Leu Ile Asn Ala Leu
65 70 75 80

Val Leu Tyr Val Gly Thr Gln Ala Ile Ala His Ile His Asn Lys Gly
85 90 95

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100 105 110

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Lys Asn Pro Ala Phe Lys Phe Trp Asn His Glu Phe Val His Cys Ala
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35 40 45

Tyr Asp Arg Tyr Thr Thr Ser Arg Arg Leu Asp Pro Ile Pro Gln Leu
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Ile Gln Cys Gln Asn Lys Gly Trp Asp Gly Tyr Asp Val Gln Trp Glu
85 90 95

Cys Lys Thr Asp Leu Asp Ile Ala Tyr Lys Phe Gly Lys Thr Val Val
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115 120 125

Ser Cys Gly Leu Glu Tyr Asn Leu Asp Tyr Thr Glu Leu Gly Leu Gln

130 135 140

Lys Leu Lys Glu Ser Gly Lys Gln His Gly Phe Ala Ser Phe Ser Asp

145 150 155 160

Tyr Tyr Tyr Lys Trp Ser Ser Ala Asp Ser Cys Asn Met Ser Gly Leu

165 170 175

Ile Thr Ile Val Val Leu Leu Gly Ile Ala Phe Val Val Tyr Lys Leu

180 185 190

Phe Leu Ser Asp Gly Gln Tyr Ser Pro Pro Pro Tyr Ser Glu Tyr Pro

195 200 205

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210 215 220

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260 265 270

Leu Gly Tyr Leu Phe Gly Ser Asn Arg Ala Ala Thr Pro Phe Ser Asp

275 280 285

Ser Trp Tyr Tyr Pro Ser Tyr Pro Pro Ser Tyr Pro Gly Thr Trp Asn

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35 40 45

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Trp Glu Thr Gly Asp Asp Arg Phe Ser Phe Arg Ser Phe Arg Ser Gly
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Leu Ser Leu Gly Thr Gln Ile Thr Tyr Ile Gly Leu Gln Phe Ile Ser

130 135 140

Phe Leu Leu Leu Leu Thr Asp Leu Leu Leu Thr Gly Asn Pro Ala Cys

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Gly Leu Lys Leu Ser Ala Phe Ala Ala Val Ser Ser Val Leu Ser Gly

165 170 175

Leu Leu Gly Met Val Ala His Met Met Tyr Ser Gln Val Phe Gln Ala

180 185 190

Thr Val Asn Leu Gly Pro Glu Asp Trp Arg Pro His Val Trp Asn Tyr

195 200 205

Gly Trp Ala Phe Tyr Met Ala Trp Leu Ser Phe Thr Cys Cys Met Ala

210 215 220

Ser Ala Val Thr Thr Phe Asn Thr Tyr Thr Arg Met Val Leu Glu Phe

225 230 235 240

Lys Cys Lys His Ser Lys Ser Phe Lys Glu Asn Pro Asn Cys Leu Pro

245 250 255

His His His Gln Cys Phe Pro Arg Arg Leu Ser Ser Ala Ala Pro Thr

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Val Gly Pro Leu Thr Ser Tyr His Gln Tyr His Asn Gln Pro Ile His

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<213> Homo sapiens

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Pro Ala Gln Gln Leu Gln Pro Gln Pro Val Ala Val Gln Gly Pro Glu
50 55 60

Pro Ala Arg Val Glu Lys Ile Phe Thr Pro Ala Ala Pro Val His Thr
65 70 75 80

Asn Lys Glu Asp Pro Ala Thr Gln Thr Asn Leu Gly Phe Ile His Ala
85 90 95

Phe Val Ala Ala Ile Ser Val Ile Ile Val Ser Glu Leu Gly Asp Lys
100 105 110

Thr Phe Phe Ile Ala Ala Ile Met Ala Met Arg Tyr Asn Arg Leu Thr
115 120 125

Val Leu Ala Gly Ala Met Leu Ala Leu Gly Leu Met Thr Cys Leu Ser
130 135 140

Val Leu Phe Gly Tyr Ala Thr Thr Val Ile Pro Arg Val Tyr Thr Tyr
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Tyr Val Ser Thr Val Leu Phe Ala Ile Phe Gly Ile Arg Met Leu Arg
165 170 175
Glu Gly Leu Lys Met Ser Pro Asp Glu Gly Gln Glu Glu Leu Glu Glu
180 185 190
Val Gln Ala Glu Leu Lys Lys Lys Asp Glu Glu Phe Gln Arg Thr Lys
195 200 205
Leu Leu Asn Gly Pro Gly Asp Val Glu Thr Gly Thr Ser Ile Thr Val
210 215 220
Pro Gln Lys Lys Trp Leu His Phe Ile Ser Pro Ile Phe Val Gln Ala
225 230 235 240
Leu Thr Leu Thr Phe Leu Ala Glu Trp Gly Asp Arg Ser Gln Leu Thr
245 250 255
Thr Ile Val Leu Ala Ala Arg Glu Asp Pro Tyr Gly Val Ala Val Gly
260 265 270
Gly Thr Val Gly His Cys Leu Cys Thr Gly Leu Ala Val Ile Gly Gly
275 280 285
Arg Met Ile Ala Gln Lys Ile Ser Val Arg Thr Val Thr Ile Ile Gly
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Trp Thr Leu Thr Asn Leu Ile His Asn Met Gly Met Tyr Ile Phe Leu
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His Thr Val Lys Gly Thr Pro Phe Glu Thr Pro Asp Gln Gly Lys Ala
65 70 75 80

Arg Leu Leu Thr His Trp Glu Gln Met Asp Tyr Gly Val Gln Phe Thr
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Ala Ser Arg Lys Phe Leu Thr Ile Thr Pro Ile Val Leu Tyr Phe Leu
100 105 110

Thr Ser Phe Tyr Thr Lys Tyr Asp Gln Ile His Phe Val Leu Asn Thr
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Val Arg Ile Phe Gly Ile Asn Lys Tyr
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35 40 45

Trp Thr Leu Thr Asn Val Ile His Asn Leu Ala Thr Tyr Val Phe Leu
50 55 60

His Thr Val Lys Gly Thr Pro Phe Glu Thr Pro Asp Gln Gly Lys Ala
65 70 75 80

Arg Leu Leu Thr His Trp Glu Gln Met Asp Tyr Gly Leu Gln Phe Thr
85 90 95

Ser Ser Arg Lys Phe Leu Ser Ile Ser Pro Ile Val Leu Tyr Leu Leu
100 105 110

Ala Ser Phe Tyr Thr Lys Tyr Asp Ala Ala His Phe Leu Ile Asn Thr
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35 40 45

Gly Thr Thr Ala Gly Phe Ser Gly Ile Phe Ser Asn Phe Leu Phe Arg

50 55 60

Arg Cys Phe Lys Val Lys His Asp Ala Leu Lys Thr Tyr Ala Ser Leu

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Ala Thr Leu Pro Phe Leu Ser Thr Val Val Thr Asp Lys Leu Phe Val

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Ile Asp Ala Leu Tyr Ser Asp Asn Ile Ser Lys Glu Asn Cys Val Phe

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Arg Ser Ser Leu Ile Gly Ile Val Cys Gly Val Phe Tyr Pro Ser Ser

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Gln Thr Gln Met Lys Leu Met Ala Ile Pro Leu Val Phe Gln Ile Met
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<213> Homo sapiens

<400> 14

atgaatgtgg gggtggcaca cagcgaagta aaccccaaca cccgagtgat gaatagccga 60

ggcatctggc tggcctacat catcttggta ggattgctgc atatggttct actcagcatc 120

cccttcttca gcattcctgt tgtctggacc ctgaccaacg tcatccataa cctggctacg 180

tatgtcttcc ttcatacggt gaaagggaca ccctttgaga ctcctgacca aggaaaggct 240

cggctactga cacactggga gcaaatggac tatgggctcc agtttacctc ttcccgcaag 300

ttcctcagca tctctcctat tgtgctctat ctcctggcca gcttctatac caagtatgat 360

gctgcgcact tcctcatcaa cacagcctca ttgctaagtg tactgctgcc gaagttgccc 420

cagttccatg gggttcgtgt ctttggcatc aacaaatac 459

<210> 15

<211> 600

<212> DNA

<213> Homo sapiens

<400> 15

atggcagcat ctatgcatgg tcagcccagt ccttctctag aagatgcaaa actcagaaga 60

ccaatggtca tagaaatcat agaaaaaaat tttgactatc ttagaaaaga aatgacacaa 120

aatatatatc aaatggcgac atttggaaca acagctggtt tctctggaat attctcaaac 180

ttcctgttca gacgctgctt caaggttaaa catgatgctt tgaagacata tgcatcattg 240

gctacacttc catttttgtc tactgttgtt actgacaagc tttttgtaat tgatgctttg 300

tattcagata atataagcaa ggaaaactgt gttttcagaa gctcactgat tggcatagtt 360

tgtggtgttt tctatcccag ttctttggct tttactaaaa atggacgcct ggcaaccaag 420

tatcataccg ttccactgcc accaaaagga agggttttaa tccattggat gacgctttgt 480

caaacacaaa tgaaattaat ggcgattcct ctagtctttc agattatgtt tggaatatta 540

aatggtctat accattatgc agtatttgaa gagacacttg agaaaactat acatgaagag 600

<210> 16

<211> 567

<212> DNA

<213> Homo sapiens

<400> 16

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ctcggggaca gggcgccact cacagccaca gccccacaac tggatgatga ggagatgtac 120

tcagcccaca tgcccgctca cctgcgctgt gatgcctgca gagctgtggc ttaccagatg 180

tggcaaaatc tggcaaaggc agagaccaaa cttcatacct caaactctgg ggggcggcgg 240

gagctgagcg agttggtcta cacggatgtc ctggaccgga gctgctcccg gaactggcag 300

gactacggag ttcgagaagt ggaccaagtg aaacgtctca caggcccagg acttagcgag 360

gggccagagc caagcatcag cgtgatggtc acaggggccc cctggcctac caggctctcc 420

aggacatgtt tgcactactt gggggagttt ggagaagacc agatctatga agcccaccaa 480

caaggccgag gggctctgga ggcattgcta tgtgggggac cccaggggc ctgctcagag 540

aaggtgtcag ccacaagaga agagctc 567

<210> 17

<211> 1167

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (187)...(903)

<400> 17

cttgcctctg ggaaggaaat acattataga gtgggaaatt tttatcattt tgaaccaaga 60

ttcttctaaa gaaagaaaga ctgattaata aaatgtggca gctgtgctct tcaaggcatt 120

tatagtgtat atagttttag aaaaacagtc ccaccactta agcatagatg taatttacta 180

ataaaa atg att ctg ctt gtg att ctt gca ttt tat ctg tgg cag gtg 228

Met Ile Leu Leu Val Ile Leu Ala Phe Tyr Leu Trp Gln Val

1 5 10

gac atg ttg agt gaa att aac att gct ccc cgg att ctc acc aat ttc 276

Asp Met Leu Ser Glu Ile Asn Ile Ala Pro Arg Ile Leu Thr Asn Phe

15 20 25 30

act gga gta atg cca cct cag ttc aaa aag gat ttg gat tcc tat ctt 324

Thr Gly Val Met Pro Pro Gln Phe Lys Lys Asp Leu Asp Ser Tyr Leu

35 40 45

aaa act cga tca cca gtc act ttc ctg tct gat ctg cgc agc aac cta 372

Lys Thr Arg Ser Pro Val Thr Phe Leu Ser Asp Leu Arg Ser Asn Leu

50 55 60

cag gta tcc aat gaa cct ggg aat cgc tac aac ctc cag ctc atc aat 420

Gln Val Ser Asn Glu Pro Gly Asn Arg Tyr Asn Leu Gln Leu Ile Asn

65 70 75

gca ctg gtg ctc tat gtc ggg act cag gcc att gcg cac atc cac aac 468
Ala Leu Val Leu Tyr Val Gly Thr Gln Ala Ile Ala His Ile His Asn
80 85 90

aag ggc agc aca cct tca atg agc acc atc act cac tca gca cac atg 516
Lys Gly Ser Thr Pro Ser Met Ser Thr Ile Thr His Ser Ala His Met
95 100 105 110

gat atc ttc cag aat ttg gct gtg gac ttg gac act gag ggt cgc tat 564
Asp Ile Phe Gln Asn Leu Ala Val Asp Leu Asp Thr Glu Gly Arg Tyr
115 120 125

ctc ttt ttg aat gca att gca aat cag ctc cgg tac cca aat agc cac 612
Leu Phe Leu Asn Ala Ile Ala Asn Gln Leu Arg Tyr Pro Asn Ser His
130 135 140

act cac tac ttc agt tgc acc atg ctg tac ctt ttt gca gag gcc aat 660
Thr His Tyr Phe Ser Cys Thr Met Leu Tyr Leu Phe Ala Glu Ala Asn
145 150 155

acg gaa gcc atc caa gaa cag atc aca aga gtt ctc ttg gaa cgg ttg 708
Thr Glu Ala Ile Gln Glu Gln Ile Thr Arg Val Leu Leu Glu Arg Leu
160 165 170

att gta aat agg cca cat cct tgg ggt ctt ctt att acc ttc att gag 756
Ile Val Asn Arg Pro His Pro Trp Gly Leu Leu Ile Thr Phe Ile Glu
175 180 185 190

ctg att aaa aac cca gcg ttt aag ttc tgg aac cat gaa ttt gta cac 804
Leu Ile Lys Asn Pro Ala Phe Lys Phe Trp Asn His Glu Phe Val His
195 200 205

tgt gcc cca gaa atc gaa aag tta ttc cag tcg gtc gca cag tgc tgc 852

Cys Ala Pro Glu Ile Glu Lys Leu Phe Gln Ser Val Ala Gln Cys Cys
210 215 220

atg gga cag aag cag gcc cag caa gta atg gaa ggg aca ggt gcc agt 900
Met Gly Gln Lys Gln Ala Gln Gln Val Met Glu Gly Thr Gly Ala Ser
225 230 235

tagacgaaac tgcatctctg ttgtacgtgt cagtctagag gtctcactgc accgagttca 960

taaactgact gaagaatcct ttcagctctt cctgactttc ccagcccttt ggtttgtggg 1020

tatctgcccc aactactgtt gggatcagcc tcctgtctta tgtgggcacg ttccaaagtt 1080

taaatgcatt tttttgactc ttggccaaaa tttagaagat gctgtgaata tcattttgaa 1140

cttgtgtaaa tacatgaaag agaaaac 1167

<210> 18

<211> 1925

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (115)...(1134)

<400> 18

gttccttcgc cgccgccagg ggtagcggtg tagctgcgca gcgtcgcgcg cgctaccgca 60

cccaggttcg gcccgtaggc gtctggcagc ccggcgccat cttcatcgag cgcc atg 117
Met
1

gcc gca gcc tgc ggg ccg gga gcg gcc ggg tac tgc ttg ctc ctc ggc 165
Ala Ala Ala Cys Gly Pro Gly Ala Ala Gly Tyr Cys Leu Leu Leu Gly
5 10 15

ttg cat ttg ttt ctg ctg acc gcg ggc cct gcc ctg ggc tgg aac gac 213
Leu His Leu Phe Leu Leu Thr Ala Gly Pro Ala Leu Gly Trp Asn Asp
20 25 30

cct gac aga atg ttg ctg cgg gat gta aaa gct ctt acc ctc cac tat 261
Pro Asp Arg Met Leu Leu Arg Asp Val Lys Ala Leu Thr Leu His Tyr
35 40 45

gac cgc tat acc acc tcc cgc agg ctg gat ccc atc cca cag ttg aaa 309
Asp Arg Tyr Thr Thr Ser Arg Arg Leu Asp Pro Ile Pro Gln Leu Lys
50 55 60 65

tgt gtt gga ggc aca gct ggt tgt gat tct tat acc cca aaa gtc ata 357
Cys Val Gly Gly Thr Ala Gly Cys Asp Ser Tyr Thr Pro Lys Val Ile
70 75 80

cag tgt cag aac aaa ggc tgg gat ggg tat gat gta cag tgg gaa tgt 405
Gln Cys Gln Asn Lys Gly Trp Asp Gly Tyr Asp Val Gln Trp Glu Cys
85 90 95

aag acg gac tta gat att gca tac aaa ttt gga aaa act gtg gtg agc 453
Lys Thr Asp Leu Asp Ile Ala Tyr Lys Phe Gly Lys Thr Val Val Ser
100 105 110

tgt gaa ggc tat gag tcc tct gaa gac cag tat gta cta aga ggt tct 501
Cys Glu Gly Tyr Glu Ser Ser Glu Asp Gln Tyr Val Leu Arg Gly Ser
115 120 125

tgt ggc ttg gag tat aat tta gat tat aca gaa ctt ggc ctg cag aaa 549

Cys Gly Leu Glu Tyr Asn Leu Asp Tyr Thr Glu Leu Gly Leu Gln Lys
130 135 140 145

ctg aag gag tct gga aag cag cac ggc ttt gcc tct ttc tct gat tat 597
Leu Lys Glu Ser Gly Lys Gln His Gly Phe Ala Ser Phe Ser Asp Tyr
150 155 160

tat tat aag tgg tcc tcg gcg gat tcc tgt aac atg agt gga ttg att 645
Tyr Tyr Lys Trp Ser Ser Ala Asp Ser Cys Asn Met Ser Gly Leu Ile
165 170 175

acc atc gtg gta ctc ctt ggg atc gcc ttt gta gtc tat aag ctg ttc 693
Thr Ile Val Val Leu Leu Gly Ile Ala Phe Val Val Tyr Lys Leu Phe
180 185 190

ctg agt gac ggg cag tat tct cct cca ccg tac tct gag tat cct cca 741
Leu Ser Asp Gly Gln Tyr Ser Pro Pro Pro Tyr Ser Glu Tyr Pro Pro
195 200 205

ttt tcc cac cgt tac cag aga ttc acc aac tca gca gga cct cct ccc 789
Phe Ser His Arg Tyr Gln Arg Phe Thr Asn Ser Ala Gly Pro Pro Pro
210 215 220 225

cca ggc ttt aag tct gag ttc aca gga cca cag aat act ggc cat ggt 837
Pro Gly Phe Lys Ser Glu Phe Thr Gly Pro Gln Asn Thr Gly His Gly
230 235 240

gca act tct ggt ttt ggc agt gct ttt aca gga caa caa gga tat gaa 885
Ala Thr Ser Gly Phe Gly Ser Ala Phe Thr Gly Gln Gln Gly Tyr Glu
245 250 255

aat tca gga cca ggg ttc tgg aca ggc ttg gga act ggt gga ata cta 933
Asn Ser Gly Pro Gly Phe Trp Thr Gly Leu Gly Thr Gly Gly Ile Leu

260 265 270

gga tat ttg ttt ggc agc aat aga gcg gca aca ccc ttc tca gac tcg 981
Gly Tyr Leu Phe Gly Ser Asn Arg Ala Ala Thr Pro Phe Ser Asp Ser

275 280 285

tgg tac tac ccg tcc tat cct ccc tcc tac cct ggc acg tgg aat agg 1029
Trp Tyr Tyr Pro Ser Tyr Pro Pro Ser Tyr Pro Gly Thr Trp Asn Arg

290 295 300 305

gct tac tca ccc ctt cat gga ggc tcg ggc agc tat tcg gta tgt tca 1077
Ala Tyr Ser Pro Leu His Gly Gly Ser Gly Ser Tyr Ser Val Cys Ser

310 315 320

aac tca gac acg aaa acc aga act gca tca gga tat ggt ggt acc agg 1125
Asn Ser Asp Thr Lys Thr Arg Thr Ala Ser Gly Tyr Gly Gly Thr Arg

325 330 335

aga cga taaagtagaa agttggagtc aaacactgga tgcagaaatt ttggatttt 1180
Arg Arg

tcatcacttt ctctttagaa aaaaagtact acctgttaac aattgggaaa aggggatatt 1240

caaaagttct gtggtgttat gtccagtgta gctttttgta ttctattatt tgaggctaaa 1300

agttgatgtg tgacaaaata cttatgtgtt gtatgtcagt gtaacatgca gatgtatatt 1360

gcagtttttg aaagtgatca ttactgtgga atgctaaaaa tacattaatt tctaaaacct 1420

gtgatgccct aagaagcatt aagaatgaag gtgttgtact aatagaaact aagtacagaa 1480

aatttcagtt ttaggtggtt gtagctgatg agttattacc tcatagagac tataatattc 1540

tatttggtat tatattattt gatgtttgct gttcttcaaa catttaaatc aagctttgga 1600

ctaattatgc taatttgtga gttctgatca cttttgagct ctgaagcttt gaatcattca 1660

gtggtggaga tggccttctg gtaactgaat attaccttct gtaggaaaag gtggaaaata 1720

agcatctaga aggttgttgt gaatgactct gtgctggcaa aaatgcttga aacctctata 1780

tttctttcgt tcataagagg taaaggtcaa atttttcaac aaaagtcttt taataacaaa 1840

agcatgcagt tctctgtgaa atctcaaata ttgttgtaat agtctgtttc aatcttaaaa 1900

agaatcaata aaaacaaaca agggg 1925

<210> 19

<211> 1125

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (71)...(1051)

<400> 19

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gacgctgacc atg gcc aag atg gag ctc tcg aag gcc ttc tct ggc cag 109

Met Ala Lys Met Glu Leu Ser Lys Ala Phe Ser Gly Gln

1 5 10

cgg aca ctc cta tct gcc atc ctc agc atg cta tca ctc agc ttc tcc 157

Arg Thr Leu Leu Ser Ala Ile Leu Ser Met Leu Ser Leu Ser Phe Ser

15 20 25

aca aca tcc ctg ctc agc aac tac tgg ttt gtg ggc aca cag aag gtg 205

Thr Thr Ser Leu Leu Ser Asn Tyr Trp Phe Val Gly Thr Gln Lys Val

30 35 40 45

ccc aag ccc ctg tgc gag aaa ggt ctg gca gcc aag tgc ttt gac atg 253
Pro Lys Pro Leu Cys Glu Lys Gly Leu Ala Ala Lys Cys Phe Asp Met
50 55 60

cca gtg tcc ctg gat gga gat acc aac aca tcc acc cag gag gtg gta 301
Pro Val Ser Leu Asp Gly Asp Thr Asn Thr Ser Thr Gln Glu Val Val
65 70 75

caa tac aac tgg gag act ggg gat gac cgg ttc tcc ttc cgg agc ttc 349
Gln Tyr Asn Trp Glu Thr Gly Asp Asp Arg Phe Ser Phe Arg Ser Phe
80 85 90

cgg agt ggc atg tgg cta tcc tgt gag gaa act gtg gaa gaa cca ggg 397
Arg Ser Gly Met Trp Leu Ser Cys Glu Glu Thr Val Glu Glu Pro Gly
95 100 105

gag agg tgc cga agt ttc att gaa ctt aca cca cca gcc aag aga gaa 445
Glu Arg Cys Arg Ser Phe Ile Glu Leu Thr Pro Pro Ala Lys Arg Glu
110 115 120 125

atc cta tgg tta tcc ctg gga acg cag atc acc tac atc gga ctt caa 493
Ile Leu Trp Leu Ser Leu Gly Thr Gln Ile Thr Tyr Ile Gly Leu Gln
130 135 140

ttc atc agc ttc ctc ctg cta cta aca gac ttg cta ctc act ggg aac 541
Phe Ile Ser Phe Leu Leu Leu Leu Thr Asp Leu Leu Leu Thr Gly Asn
145 150 155

cct gcc tgt ggg ctc aaa ctg agc gcc ttt gct gct gtt tcc tct gtc 589
Pro Ala Cys Gly Leu Lys Leu Ser Ala Phe Ala Ala Val Ser Ser Val
160 165 170

ctg tca ggt ctc ctg ggg atg gtg gcc cac atg atg tat tca caa gtc 637

Leu Ser Gly Leu Leu Gly Met Val Ala His Met Met Tyr Ser Gln Val
175 180 185

ttc caa gcg act gtc aac ttg ggt cca gaa gac tgg aga cca cat gtt 685
Phe Gln Ala Thr Val Asn Leu Gly Pro Glu Asp Trp Arg Pro His Val
190 195 200 205

tgg aat tat ggc tgg gcc ttc tac atg gcc tgg ctc tcc ttc acc tgc 733
Trp Asn Tyr Gly Trp Ala Phe Tyr Met Ala Trp Leu Ser Phe Thr Cys
210 215 220

tgc atg gcg tcg gct gtc acc acc ttc aac acg tac acc agg atg gtg 781
Cys Met Ala Ser Ala Val Thr Thr Phe Asn Thr Tyr Thr Arg Met Val
225 230 235

ctg gag ttc aag tgc aag cat agt aag agc ttc aag gaa aac ccg aac 829
Leu Glu Phe Lys Cys Lys His Ser Lys Ser Phe Lys Glu Asn Pro Asn
240 245 250

tgc cta cca cat cac cat cag tgt ttc cct cgg cgg ctg tca agt gca 877
Cys Leu Pro His His His Gln Cys Phe Pro Arg Arg Leu Ser Ser Ala
255 260 265

gcc ccc acc gtg ggt cct ttg acc agc tac cac cag tat cat aat cag 925
Ala Pro Thr Val Gly Pro Leu Thr Ser Tyr His Gln Tyr His Asn Gln
270 275 280 285

ccc atc cac tct gtc tct gag gga gtc gac ttc tac tcc gag ctg cgg 973
Pro Ile His Ser Val Ser Glu Gly Val Asp Phe Tyr Ser Glu Leu Arg
290 295 300

aac aag gga ttt caa aga ggg gcc agc cag gag ctg aaa gaa gca gtt 1021
Asn Lys Gly Phe Gln Arg Gly Ala Ser Gln Glu Leu Lys Glu Ala Val

305 310 315

agg tca tct gta gag gaa gag cag tgt taggagttaa gcgggtttgg gg 1070

Arg Ser Ser Val Glu Glu Glu Gln Cys

320 325

agtaggcttg agccctacct tacacgtctg ctgattatca acatgtgctt aagcc 1125

<210> 20

<211> 1734

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (40)...(1014)

<400> 20

ctcttgcggc gcccgtgcgc ggccggcccg gcaggcggg atg gcg gcc gcg gct 54

Met Ala Ala Ala Ala

1 5

ccg ggg aac ggc cgc gca tcg gcg ccc cgg ctg ctt ctg ctc ttt ctg 102

Pro Gly Asn Gly Arg Ala Ser Ala Pro Arg Leu Leu Leu Leu Phe Leu

10 15 20

gtt ccg ctg ctg tgg gcc ccg gct gcg gtc cgg gcc ggc cca gat gaa 150

Val Pro Leu Leu Trp Ala Pro Ala Ala Val Arg Ala Gly Pro Asp Glu

25 30 35

gac ctt agc cac cgg aac aaa gaa ccg ccg gcg ccg gcc cag cag ctg 198
Asp Leu Ser His Arg Asn Lys Glu Pro Pro Ala Pro Ala Gln Gln Leu
40 45 50

cag ccg cag cct gtg gct gtg cag ggc ccc gag ccg gcc cgg gtc gag 246
Gln Pro Gln Pro Val Ala Val Gln Gly Pro Glu Pro Ala Arg Val Glu
55 60 65

aaa ata ttt aca cca gca gct cca gtt cat acc aat aaa gaa gat cct 294
Lys Ile Phe Thr Pro Ala Ala Pro Val His Thr Asn Lys Glu Asp Pro
70 75 80 85

gct acc caa act aat ttg gga ttt atc cat gca ttt gtc gct gcc ata 342
Ala Thr Gln Thr Asn Leu Gly Phe Ile His Ala Phe Val Ala Ala Ile
90 95 100

tca gtt att att gta tct gaa ttg ggt gat aag aca ttt ttt ata gca 390
Ser Val Ile Ile Val Ser Glu Leu Gly Asp Lys Thr Phe Phe Ile Ala
105 110 115

gcc atc atg gca atg cgc tat aac cgc ctg acc gtg ctg gct ggt gca 438
Ala Ile Met Ala Met Arg Tyr Asn Arg Leu Thr Val Leu Ala Gly Ala
120 125 130

atg ctt gcc ttg gga cta atg aca tgc ttg tca gtt ttg ttt ggc tat 486
Met Leu Ala Leu Gly Leu Met Thr Cys Leu Ser Val Leu Phe Gly Tyr
135 140 145

gcc acc aca gtc atc ccc agg gtc tat aca tac tat gtt tca act gta 534
Ala Thr Thr Val Ile Pro Arg Val Tyr Thr Tyr Tyr Val Ser Thr Val
150 155 160 165

tta ttt gcc att ttt ggc att aga atg ctt cgg gaa ggc tta aag atg 582

Leu Phe Ala Ile Phe Gly Ile Arg Met Leu Arg Glu Gly Leu Lys Met
170 175 180

agc cct gat gag ggt caa gag gaa ctg gaa gaa gtt caa gct gaa tta 630
Ser Pro Asp Glu Gly Gln Glu Glu Leu Glu Glu Val Gln Ala Glu Leu
185 190 195

aag aag aaa gat gaa gaa ttt caa cga acc aaa ctt tta aat gga ccg 678
Lys Lys Lys Asp Glu Glu Phe Gln Arg Thr Lys Leu Leu Asn Gly Pro
200 205 210

gga gat gtt gaa acg ggt aca agc ata aca gta cct cag aaa aag tgg 726
Gly Asp Val Glu Thr Gly Thr Ser Ile Thr Val Pro Gln Lys Lys Trp
215 220 225

ttg cat ttt att tca ccc att ttt gtt caa gct ctt aca tta aca ttc 774
Leu His Phe Ile Ser Pro Ile Phe Val Gln Ala Leu Thr Leu Thr Phe
230 235 240 245

tta gca gaa tgg ggt gat cgc tct caa cta act aca att gta ttg gca 822
Leu Ala Glu Trp Gly Asp Arg Ser Gln Leu Thr Thr Ile Val Leu Ala
250 255 260

gct aga gag gac ccc tat ggt gta gcc gtg ggt gga act gtg ggg cac 870
Ala Arg Glu Asp Pro Tyr Gly Val Ala Val Gly Gly Thr Val Gly His
265 270 275

tgc ctg tgc acg gga ttg gca gta att gga gga aga atg ata gca cag 918
Cys Leu Cys Thr Gly Leu Ala Val Ile Gly Gly Arg Met Ile Ala Gln
280 285 290

aaa atc tct gtc aga act gtg aca atc ata gga ggc atc gtt ttt ttg 966
Lys Ile Ser Val Arg Thr Val Thr Ile Ile Gly Gly Ile Val Phe Leu

295 300 305

gcg ttt gca ttt tct gca cta ttt ata agc cct gat tct ggt ttt 1011

Ala Phe Ala Phe Ser Ala Leu Phe Ile Ser Pro Asp Ser Gly Phe

310 315 320

taacgctgt ttgttcatct atatttagtt taaaataggt agtattatct ttctgtacat 1070

agtgtacatt acaactaaaa gtgatggaaa aatactgtat tttgtagcac tgattttgtg 1130

agtttgaccc attattatgt ctgagatata atcattgatt ctatttgtaa caaggagttt 1190

taaaagaaac ctgacttcta agtgtgggtt tttcttctct ccaacataat tatgttaata 1250

tggtcctcat ttttcttttg gtgcagaacc gttgtgcagt ggggtctacc atgcaatttt 1310

ctttcagcac tgacccctttt ttaaggaata caaattttct ccttcatcac ttaggtgttt 1370

taagatgttt accttaaagt ttttcttggg gaaagaatga attaatttct atttcttaaa 1430

acatttccct gagccagtaa acagtagttt aatcattggt cttttcaaaa ctaggtgttt 1490

aaaaaaagag acatatatga tattgctgtt atatcaataa catggcacaa caagaactgt 1550

ctgccaggtc attcttcctc ttttttttttt aattgggtag gacacccaat ataaaaacag 1610

tcaatatttg acaatgtgga attaccaaat taaaagagaa tactatgaat gtattcatat 1670

tttttctata ttgaataaac aatgtaacat agataacaat ataaataaaa gtggtatgac 1730

cagt 1734

<210> 21

<211> 2064

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (98)...(559)

<400> 21

aaaacagctg ctggagcagc agcggccccc gctcccggga accgttcccg ggccgttgat 60

cttcggcccc acacgaacag cagagagggg cagcagg atg aat gtg ggc aca 112
Met Asn Val Gly Thr
1 5

gcg cac agc gag gtg aac ccc aac acg cgg gtg atg aac agc cgt ggc 160
Ala His Ser Glu Val Asn Pro Asn Thr Arg Val Met Asn Ser Arg Gly
10 15 20

atc tgg ctc tcc tac gtg ctg gcc atc ggt ctc ctc cac atc gtg ctg 208
Ile Trp Leu Ser Tyr Val Leu Ala Ile Gly Leu Leu His Ile Val Leu
25 30 35

ctg agc atc ccg ttt gtg agt gtc cct gtc gtc tgg acc ctc acc aac 256
Leu Ser Ile Pro Phe Val Ser Val Pro Val Val Trp Thr Leu Thr Asn
40 45 50

ctc att cac aac atg ggc atg tat atc ttc ctg cac acg gtg aag ggg 304
Leu Ile His Asn Met Gly Met Tyr Ile Phe Leu His Thr Val Lys Gly
55 60 65

aca ccc ttt gag acc ccg gac cag ggc aag gcg agg ctg cta acc cac 352
Thr Pro Phe Glu Thr Pro Asp Gln Gly Lys Ala Arg Leu Leu Thr His
70 75 80 85

tgg gag cag atg gat tat ggg gtc cag ttc acg gcc tct cgg aag ttc 400
Trp Glu Gln Met Asp Tyr Gly Val Gln Phe Thr Ala Ser Arg Lys Phe
90 95 100

ttg acc atc aca ccc atc gtg ctg tac ttc ctc acc agc ttc tac act 448
Leu Thr Ile Thr Pro Ile Val Leu Tyr Phe Leu Thr Ser Phe Tyr Thr
105 110 115

aag tac gac cag atc cat ttt gtg ctc aac acc gtg tcc ctg atg agc 496
Lys Tyr Asp Gln Ile His Phe Val Leu Asn Thr Val Ser Leu Met Ser
120 125 130

gtg ctt atc ccc aag ctg ccc cag ctc cac gga gtc cgg att ttt gga 544
Val Leu Ile Pro Lys Leu Pro Gln Leu His Gly Val Arg Ile Phe Gly
135 140 145

atc aat aag tac tgagagtgca gccccttccc ctgcccaggg tggcagggga gggg 600
Ile Asn Lys Tyr
150

tagggtaaaa ggcatgtgct gcaacactga agacagaaag aagaagcctc tggacactgc 660
cagagatggg ggttgagcct ctggcctaat ttccccctc gcttccccca gtagccaact 720
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<211> 570

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<213> Homo sapiens

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Met Asn Val Gly Val Ala His Ser

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gaa gta aac ccc aac acc cga gtg atg aat agc cga ggc atc tgg ctg      99
Glu Val Asn Pro Asn Thr Arg Val Met Asn Ser Arg Gly Ile Trp Leu
    10                  15                  20

gcc tac atc atc ttg gta gga ttg ctg cat atg gtt cta ctc agc atc     147
Ala Tyr Ile Ile Leu Val Gly Leu Leu His Met Val Leu Leu Ser Ile
25                  30                  35                  40

ccc ttc ttc agc att cct gtt gtc tgg acc ctg acc aac gtc atc cat     195
Pro Phe Phe Ser Ile Pro Val Val Trp Thr Leu Thr Asn Val Ile His
                45                  50                  55

aac ctg gct acg tat gtc ttc ctt cat acg gtg aaa ggg aca ccc ttt     243
Asn Leu Ala Thr Tyr Val Phe Leu His Thr Val Lys Gly Thr Pro Phe
            60                  65                  70

gag act cct gac caa gga aag gct cgg cta ctg aca cac tgg gag caa     291
Glu Thr Pro Asp Gln Gly Lys Ala Arg Leu Leu Thr His Trp Glu Gln
        75                  80                  85

atg gac tat ggg ctc cag ttt acc tct tcc cgc aag ttc ctc agc atc     339
Met Asp Tyr Gly Leu Gln Phe Thr Ser Ser Arg Lys Phe Leu Ser Ile
    90                  95                  100

tct cct att gtg ctc tat ctc ctg gcc agc ttc tat acc aag tat gat     387
Ser Pro Ile Val Leu Tyr Leu Leu Ala Ser Phe Tyr Thr Lys Tyr Asp
105                 110                 115                 120

gct gcg cac ttc ctc atc aac aca gcc tca ttg cta agt gta ctg ctg     435
Ala Ala His Phe Leu Ile Asn Thr Ala Ser Leu Leu Ser Val Leu Leu
                125                 130                 135
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ccg aag ttg ccc cag ttc cat ggg gtt cgt gtc ttt ggc atc aac aaa 483
Pro Lys Leu Pro Gln Phe His Gly Val Arg Val Phe Gly Ile Asn Lys
140 145 150

tac tgag ggatgggttt tgggacagct ccatgggcat ggggaaggca ctgaaacaga 540
Tyr

ggactataaa acatccttct cttattctcc 570

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gaacttaatc tttcatgaga aactgaggat agagatgtca ataagcagcc actgtttcca 180

cctccccacc tgaagagcta ggaggacaac tacaaagagc ctgactgcct tctcggaatg 240

aggagagagg aaaacagcaa cagtatcagt tttcaag atg gca gca tct atg 292
Met Ala Ala Ser Met
1 5

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cat ggt cag ccc agt cct tct cta gaa gat gca aaa ctc aga aga cca      340
His Gly Gln Pro Ser Pro Ser Leu Glu Asp Ala Lys Leu Arg Arg Pro
                10                  15                  20

atg gtc ata gaa atc ata gaa aaa aat ttt gac tat ctt aga aaa gaa      388
Met Val Ile Glu Ile Ile Glu Lys Asn Phe Asp Tyr Leu Arg Lys Glu
            25                  30                  35

atg aca caa aat ata tat caa atg gcg aca ttt gga aca aca gct ggt      436
Met Thr Gln Asn Ile Tyr Gln Met Ala Thr Phe Gly Thr Thr Ala Gly
        40                  45                  50

ttc tct gga ata ttc tca aac ttc ctg ttc aga cgc tgc ttc aag gtt      484
Phe Ser Gly Ile Phe Ser Asn Phe Leu Phe Arg Arg Cys Phe Lys Val
    55                  60                  65

aaa cat gat gct ttg aag aca tat gca tca ttg gct aca ctt cca ttt      532
Lys His Asp Ala Leu Lys Thr Tyr Ala Ser Leu Ala Thr Leu Pro Phe
70                  75                  80                  85

ttg tct act gtt gtt act gac aag ctt ttt gta att gat gct ttg tat      580
Leu Ser Thr Val Val Thr Asp Lys Leu Phe Val Ile Asp Ala Leu Tyr
                90                  95                  100

tca gat aat ata agc aag gaa aac tgt gtt ttc aga agc tca ctg att      628
Ser Asp Asn Ile Ser Lys Glu Asn Cys Val Phe Arg Ser Ser Leu Ile
            105                 110                 115

ggc ata gtt tgt ggt gtt ttc tat ccc agt tct ttg gct ttt act aaa      676
Gly Ile Val Cys Gly Val Phe Tyr Pro Ser Ser Leu Ala Phe Thr Lys
        120                 125                 130

aat gga cgc ctg gca acc aag tat cat acc gtt cca ctg cca cca aaa      724
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Asn Gly Arg Leu Ala Thr Lys Tyr His Thr Val Pro Leu Pro Pro Lys
135 140 145

gga agg gtt tta atc cat tgg atg acg ctt tgt caa aca caa atg aaa 772
Gly Arg Val Leu Ile His Trp Met Thr Leu Cys Gln Thr Gln Met Lys
150 155 160 165

tta atg gcg att cct cta gtc ttt cag att atg ttt gga ata tta aat 820
Leu Met Ala Ile Pro Leu Val Phe Gln Ile Met Phe Gly Ile Leu Asn
170 175 180

ggt cta tac cat tat gca gta ttt gaa gag aca ctt gag aaa act ata 868
Gly Leu Tyr His Tyr Ala Val Phe Glu Glu Thr Leu Glu Lys Thr Ile
185 190 195

cat gaa gag taaccaaaaa aatgaatggt tgctaactta gcaaaatgaa gtt 920
His Glu Glu
200

tctataaaga ggactcaggc attgctgaaa gagttaaaag taactgtgaa caaataattt 980

gttctgtgcc ttttgcctgg tatatagcaa atactcaaaa agtattcaat aattcaatca 1040

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Met Arg Leu Ser Leu Pro Leu Leu Leu Leu Leu Gly Ala Trp Ala
1 5 10 15

atc cca ggg ggc ctc ggg gac agg gcg cca ctc aca gcc aca gcc cca 153
Ile Pro Gly Gly Leu Gly Asp Arg Ala Pro Leu Thr Ala Thr Ala Pro
20 25 30

caa ctg gat gat gag gag atg tac tca gcc cac atg ccc gct cac ctg 201
Gln Leu Asp Asp Glu Glu Met Tyr Ser Ala His Met Pro Ala His Leu
35 40 45

cgc tgt gat gcc tgc aga gct gtg gct tac cag atg tgg caa aat ctg 249
Arg Cys Asp Ala Cys Arg Ala Val Ala Tyr Gln Met Trp Gln Asn Leu
50 55 60

gca aag gca gag acc aaa ctt cat acc tca aac tct ggg ggg cgg cgg 297
Ala Lys Ala Glu Thr Lys Leu His Thr Ser Asn Ser Gly Gly Arg Arg
65 70 75 80

gag ctg agc gag ttg gtc tac acg gat gtc ctg gac cgg agc tgc tcc 345
Glu Leu Ser Glu Leu Val Tyr Thr Asp Val Leu Asp Arg Ser Cys Ser
85 90 95

cgg aac tgg cag gac tac gga gtt cga gaa gtg gac caa gtg aaa cgt 393

Arg Asn Trp Gln Asp Tyr Gly Val Arg Glu Val Asp Gln Val Lys Arg

100 105 110

ctc aca ggc cca gga ctt agc gag ggg cca gag cca agc atc agc gtg 441

Leu Thr Gly Pro Gly Leu Ser Glu Gly Pro Glu Pro Ser Ile Ser Val

115 120 125

atg gtc aca ggg ggc ccc tgg cct acc agg ctc tcc agg aca tgt ttg 489

Met Val Thr Gly Gly Pro Trp Pro Thr Arg Leu Ser Arg Thr Cys Leu

130 135 140

cac tac ttg ggg gag ttt gga gaa gac cag atc tat gaa gcc cac caa 537

His Tyr Leu Gly Glu Phe Gly Glu Asp Gln Ile Tyr Glu Ala His Gln

145 150 155 160

caa ggc cga ggg gct ctg gag gca ttg cta tgt ggg gga ccc cag ggg 585

Gln Gly Arg Gly Ala Leu Glu Ala Leu Leu Cys Gly Gly Pro Gln Gly

165 170 175

gcc tgc tca gag aag gtg tca gcc aca aga gaa gag ctc tagtcc 630

Ala Cys Ser Glu Lys Val Ser Ala Thr Arg Glu Glu Leu

180 185

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agcctcaggg cactcgggcc tgggtgggag tcaacgcctt cccctctgga ctcaaataaa 810

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